Functional motor disorders: mechanism, prognosis and treatment

Gelauff, Jeannette

DOI:
10.33612/diss.136733110

Functional Motor Disorders: mechanism, prognosis and treatment

Jeannette M. Gelauff

Colofon
Functional Motor Disorders: mechanism, prognosis and treatment, by Jeannette Gelauff
ISBN: 978-94-034-2487-3
E-book: ISBN: 978-94-034-2488-0

Printed by Ipskamp Printing, proefschriften.net
Layout and design by Lara Leijtens, persoonlijkproefschrift.nl
Illustrations for chapters 1,2,3,4,5,6,8 and 10 (containing original data) were made by Ruben Maalman, www.rubenmaalman.nl

Cover: Burdened Children 1930; Paul Klee 1879-1940; T06796 ©Tate, London 2018
A detail from the same artwork is used in each part of this thesis

Op de voorkant van dit proefschrift staat een afbeelding van een schilderij van Paul Klee (1879-1940) uit 1930, genaamd Belastete Kinder. Het schilderij is in bezit van het Tate in London. Hier wordt het kunstwerk getypeerd als: 'taking a line for a walk'. Het schilderij lijkt te bestaan uit een grotendeels ononderbroken lijn, die zowel beweging als veelzijdigheid uitstraalt.
Om die reden is deze afbeelding gekozen: Observatie van beweging is essentieel bij het diagnosticeren van bewegingsstoornissen. Ook moet er aandacht zijn voor de vele facetten waaruit de patiënt bestaat, hiervoor zijn soms de perspectieven van verschillende specialisaties nodig. Daarnaast past deze afbeelding goed bij hoofdstuk 5, waarin we onder andere de beleving van het lichaamsschema van patiënten onderzoeken.

I am very thankful for the financial support of the following sponsors:
GSMS graduate school University of Groningen, De Stichting De Cock -Hadders, UMCG Pilot Doelmatigheid HAP subsidie, stichting MIND (voorheen Fonds Psychische Gezondheid) en de dystonie-vereniging.

rijksuniversiteit groningen

Functional Motor Disorders: mechanism, prognosis and treatment

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 28 oktober 2020 om 18.00 uur

door

Jeannette M. Gelauff

geboren op 9 november 1987
te Voorburg

PROMOTORES

Prof. dr. M.A.J. de Koning-Tijssen
Prof. dr. J.G.M. Rosmalen
Prof. dr. J. Stone

BEOORDELINGSCOMMISSIE

Prof. dr. T. van Laar
Prof. dr. O.A. van den Heuvel
Prof. dr. M. Edwards

PARANIMFEN

Arthur Buijink
Anouk Kuiper

TABLE OF CONTENTS

Introduction

Partly based on:

1. Gelauff JM, Stone J. Chapter 33. Approach to the Patient with Functional Disorders in the Neurology Clinic. Practical Neurology 2017. Fifth edition, edited by José Biller.
2. Lehn A, Gelauff JM, Hoeritzauer I, Ludwig L, McWhirter L, Williams S, Gardiner P, Carson A, Stone J Functional neurological disorders: mechanisms and treatment. J Neurol 2015.

Functional motor disorders (FMD) consist of involuntary movements, posturing, gait disorder and paresis. They are defined by signs that demonstrate the functional nature of the mechanism like variability, influence of attention and distraction and incongruity with anatomical boundaries. FMD exists at the interface between neurology and psychiatry. Functional motor disorders are part of the broader group of functional neurological disorders (FND). FND account for between 15-30% of neurology outpatients depending how they are defined and may co-exist with neurological disease [1–4]. Having FMD often impacts the lives of patients to a large extent Quality of life and impairment have been found to be comparable to disabling neurological conditions like Parkinson's disease [5] and Multiple Sclerosis [6].

At the start of this thesis, the clinical research field of functional neurological disorders was rapidly changing. New insights changed the leading theories on the mechanism, diagnosis and approach to patients with FMD. This has been pivotal for the composition of this thesis, which explores the mechanism, prognosis (natural history) and treatment of FMD. Therefore these important developments in the field are briefly discussed below, followed by an outline of the thesis.

THE NEW NORMAL

What we call "functional neurological disorder" now, has been in and out of fashion within academic circles over the centuries. Interestingly, the symptoms of patients with FND in neurology clinics nowadays are highly comparable to historical descriptions and photos. For example the presentation of functional limb weakness through the 18th to 20th century is strikingly similar to the present with the typical dragging gate, the same inconsistencies in the examination, and highly comparable precipitating factors [7]. However, the concepts explaining these symptoms and the names they were given were subject to change, which means parallels cannot always be drawn in a meaningful way. Take *Shell shock*, a disorder soldiers suffered from in the 20th century as a result of the traumatic experience of fighting in the trenches. It most likely comprised post-traumatic stress disorder, functional neurological symptoms, physical injury, head injury and possibly also malingering [8].

In the 19th century, interest in *hysteria* (a word originating from ancient Greek and referring to mostly women suffering from neurological and/or emotional symptoms) came to a head when the prominent physician Charcot, who led L'hospital de Salpêtrière in Paris, started studying large numbers of patients. Demonstrations

of his patients were attended by many influential physicians who would later become the founders of modern day neurology and psychiatry, but they became so popular that even non-medical spectators visited the hospital. Charcot focused on clinical observation of the symptoms, and explained the disorder to be originating from a "dynamic" or "functional" lesion of the central nervous system [9]. Freud, who developed an interest in hysteria after his stay with Charcot, developed the conversion theory, which hypothesised that repressed traumatic experiences (abuse, and in his later work sexual abuse or sexual fantasies) were converted into physical symptoms [10]. This theory was not confirmed by experimental studies, but nevertheless had a major impact on the general view on functional disorders. Due to several factors - amongst them the growing detachment of neurology and psychiatry - attention to functional neurological disorders reduced after the first world war, especially within neurology [11].

In the last two decades, a small (but currently growing) number of physicians and psychologists showed renewed interest in patients with functional neurological symptoms. They realised that patients were often left undiagnosed and received very limited care, because the underlying cause of their symptoms was seen as 'non-organic' or 'psychiatric' (ref Edwards, Stone, Sharpe), although they suffered from neurological symptoms. A 'normal' approach to the patient, in which the neurologist takes a history focused on the symptoms, performs full physical examination and provides an explanation of the symptoms and their cause, would overcome a large part of the difficulty experienced by both patients [12,13] and physicians [14–17]. This insight has led to a paradigm shift whereby neurologists base the diagnosis of functional neurological symptoms on positive signs in history and examination and ideally take responsibility in organizing treatment. A 'new normal' [18–20].

Based on observation and experimental studies, the pathophysiology of FMD has been updated as well. This is best understood when the aetiology and the mechanism are separated. The aetiology is a model with biological, social and psychological factors that either play a role in predisposing, precipitating or perpetuating the functional symptoms. In each patient a different composition of factors is assumed to be present [20], many factors still remain unknown. The mechanism of FMD is best explained in the landmark paper of Edwards et al. [21]. The paper describes a Bayesian model based on the principle that the brain is not a sole machine of input and programmed response, but a hierarchical system that bases its actions on prior beliefs (or expectations) and updates these through sensory input [22–24]. Functional disorders are no longer seen as a black box with the 'cause' (for example childhood

trauma) going in (at any given time in the past) and physical symptoms coming out. The new concept is more complex: aetiological factors contribute to a set of prior beliefs (for example 'when I have severe symptoms, this means something important must be damaged') that create vulnerability for developing a functional disorder, once confronted with the right trigger (for example severe backpain after a car accident). These ***beliefs*** or ***expectations*** are the basis of programmed responses in the brain. There are several (not necessarily mutually exclusive) theories on the formation of beliefs and the consequent development of motor symptoms in FMD. There are clues that the phenomenon of modelling disorders witnessed in one's environment could play a role (ref). However, such studies are prone for recall bias. Another illustration on how specific symptoms are likely to result from beliefs, is that the presentation of functional symptoms are partly in line with common belief about the presentation of neurological symptoms. And, like in many mental disorders, traumatic experiences (for example in childhood) cause a stress reaction that most likely alters expectations and with that, an altered programmed response in the brain towards future triggers. It is hypothesised, amongst others based on imaging findings [25], that the above prior beliefs influence perception of sensory input and motor output by altering the mapped representations (top-down) of the body and bodily perceptions (and most likely also the outside world).

Attention and sense of agency are key elements within the Bayesian framework, which are distorted as a consequence of prior beliefs or vice versa. The element of attention is expressed clearly in clinical practice, as symptoms abate temporarily when patients are distracted [26,27]. Altered sense of agency has been found in several experimental studies. In two different experiments the experience of intention before a movement was distorted in patients with FMD [28,29]. Sensory attenuation, a measure of motor agency, is impaired in FMD: When performing a force matching task, healthy controls overestimate the force required when pressing directly on their own finger, but patients do not [30]. Using clinical neurophysiology, abnormal sense of voluntariness in FMD was found. Abnormal preparation of intended voluntary movements with an often absent Bereitschaftspotential was demonstrated, while the functional movement symptoms that are perceived involuntary by the patient (in this study jerky movements), were preceded by normal preparation and a present Bereitschaftspotential [31]. Imaging studies have implicated the role of the temporoparietal junction in this altered sense of agency, amongst others in a task comparing functional tremor with simulated tremor in the same individuals [32]. More generally results from fMRI studies suggest an association between emotional processing and motor planning and/or execution, because they have

shown connectivity between the supplementary motor area and the amygdala in emotional tasks [33,34] and a simple motor task [25]. Another area found to be involved in several imaging studies is the insula, a multi-functional brain region involved in emotion regulation and self-awareness amongst others [25,33,35,36].

The treatment approach to patients with FMD has changed accordingly. A stepped care model has been proposed [37], in which explanation of the disorder by the neurologist is an essential first step. Inconsistencies in the presentation of symptoms, that were previously used to point out non-organicity, were now proposed to be helpful in the explanation of the disorder to the patient [38]. Further effective treatments have a strong emphasis on relearning normal movements, for example using physiotherapy [39] or in a multidisciplinary setting [40–43]. In addition, psychological treatment can be added that has expanded from predominantly psychodynamic to cognitive behavioural or acceptance and commitment oriented therapy.

NEW QUESTIONS

New research findings and altered theories elicit many new research questions. In light of these developments, this thesis addresses questions about mechanism, prognosis and treatment.

From a mechanistic point of view, defining the clinical picture in a more detailed manner could provide new insights. Patients often experience non-motor symptoms in addition to the functional motor symptoms. Fatigue, for example, seems very prominent in clinical practice. It is of interest to investigate the severity of common non-motor symptoms: fatigue, pain, depression and anxiety and their influence on health related quality of life, compared to other neurological disorders. And, are these non-motor symptoms the same for all different functional motor disorders?

Furthermore, from the proposed mechanism by Edwards et al, the topics of distorted self-agency and abnormal attention to the self (or more specifically towards the symptoms) need to be further substantiated. Which brain networks are involved in the distorted perception of self-agency and how do they relate to abnormal attentional processes and perception of body scheme?

A better knowledge on the prognosis (natural history) of the symptoms of FMD and the course of quality of life in time are important to answer patients' questions and

to interpret outcomes of clinical trials. Do the symptoms usually resolve (as is a commonly held belief by many physicians, although not substantiated)? Does the diagnosis often change? Could we find a way to predict an individual's chance of a positive outcome?

Ultimately, the clinical aim is to find better treatments for FMD patients. Especially as the prognosis appears to be poor, effective treatments are needed. To start with, no trials have been performed to test the hypothesis that explanation is important as the first step in treatment. Would that lead to overall better outcomes and perhaps more effective further treatments?

In this thesis, the above questions will be addressed in the following order.

OUTLINE

Part 1:

Mechanism

In order to better understand FMD, we need a clearer picture of the (variability of) clinical syndromes that patients present with. At the same time, experiments should be designed to disentangle the underlying mechanism.

Clinical aspects

In this thesis we compare non-motor features, triggers and demographics between groups of different functional motor symptoms in **chapter 1**. Furthermore we explore the severity of fatigue - and its influence on quality of life - in FMD compared to organic neuromuscular disorders, in **chapter 2.** For chapter 1 and 2 baseline data of the trial described in chapter 10 was used. We compared non-motor features between patients with functional and organic myoclonus in **chapter 3.**

Experimental aspects

Three experiments were performed. First, to further explore the concept of self-agency, an experiment was performed where incongruence between of motor action and sensory response was used to compare patients with functional myoclonus or tremor and healthy controls **(chapter 4).** Secondly, **Chapter 5** investigates the concepts of self-agency and perception of body scheme using a previously developed fMRI paradigm. In this study the same patients as in the above-mentioned agency experiment, were scanned during a task comparing self-referenced versus goal

directed and self-initiated versus fixed movement. Thirdly, we performed a resting-state fMRI study to compare brain activity at rest between FMD and healthy controls, in the same subset of patients, in **chapter 6** a data-driven approach using independent component analysis was used, forming networks of brain activity.

Part 2:

Prognosis

Knowledge on the prognosis of functional motor disorders is mainly based on small, retrospective studies which show variable but overall poor outcome. In this thesis, a systematic review summarizing the literature on the prognosis of functional motor disorders is included **as chapter 7.** We performed a 14 year follow-up study of patients with functional paresis, currently the longest systematic follow-up study in the literature, the results are displayed in **chapter 8.** Issues including misdiagnosis, mortality, symptom outcome and quality of life are studied and discussed here.

Part 3:

Treatment

Treatment options for patients with FMD are scarce and evidence on effective treatments is limited, mainly due to the small number of studies performed in the field, and the quality of the available studies. **In chapter 9** the literature at the start of this thesis is summarised in a review on the treatment of FMD. To enhance the first step of treatment - explanation of the disorder by the neurologist - we designed a new website with education and self-help. The effect of this website on self-rated general health and a number of secondary outcomes, was studied in a randomised controlled trial in patients with FMD and the results are reported in **chapter 10.**

In the general discussion the findings are interpreted and implications for the future are described.

Terminology

In ancient times, *hysteria* was used for symptoms comparable to (but not limited to) functional neurological disorders, but this term is abandoned for obvious reasons. *Psychosomatic*, *psychogenic, somatization* and *conversion disorder* all imply a dominantly psychological etiology or the conversion of psychological distress into physical symptoms. Studies show higher rates of psychological comorbidity, and some useful treatments are psychological. However psychological factors in the etiology are now seen as risk factors that can contribute to the development of a functional motor disorder, but not the sole cause. *Non-organic (e.g. non-epileptic)* and *medically unexplained* label the problem by what it is not. This is not helpful for patients. Also, these terms imply a strict separation between functional disorders and other neurological disorders, while many conditions in neurology have a largely unknown etiology. The term *functional neurological disorder* emphasizes a disorder of function without assuming aetiology. It also has been found to be more acceptable to patients [13], where other terms are perceived as being offensive. In this thesis therefore we will use functional neurological disorder (FND), and when referring to motor symptoms *functional motor disorder (FMD)* or in some chapters *motor FND,* conform DSM-5.

REFERENCES

1. A.J. Carson, B. Ringbauer, J. Stone, L. McKenzie, C. Warlow, M. Sharpe, Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics, J. Neurol. Neurosurg. Psychiatry. 68 (2000) 207.
2. S. Reid, S. Wessely, T. Crayford, M. Hotopf, Medically unexplained symptoms in frequent attenders of secondary health care: retrospective cohort study, BMJ. 322 (2001) 767.
3. P. Fink, H.M. Steen, L. Sondergaard, Somatoform disorders among first-time referrals to a neurology service, Psychosomatics. 46 (2005) 540–548.
4. T. Lempert, M. Dieterich, D. Huppert, T. Brandt, Psychogenic disorders in neurology: frequency and clinical spectrum, Acta Neurol.Scand. 82 (1990) 335–340.
5. K.E. Anderson, A.L. Gruber-Baldini, C.G. Vaughan, S.G. Reich, P.S. Fishman, W.J. Weiner, L.M. Shulman, Impact of psychogenic movement disorders versus Parkinson's on disability, quality of life, and psychopathology, Mov Disord. 22 (2007) 2204–2209. doi:10.1002/mds.21687.
6. J. Stone, C. Warlow, M. Sharpe, The symptom of functional weakness: A controlled study of 107 patients, Brain. 133 (2010) 1537–1551. doi:10.1093/brain/awq068.
7. C.G. Goetz, Charcot, hysteria, and simulated disorders, Handb. Clin. Neurol. 139 (2016) 11–23. doi:10.1016/B978-0-12-801772-2.00002-3.
8. M.A. Crocq, L. Crocq, From shell shock and war neurosis to posttraumatic stress disorder: a history of psychotraumatology., Dialogues Clin. Neurosci. 2 (2000) 47–55. http://www.ncbi.nlm.nih.gov/pubmed/22033462%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3181586.
9. Charcot, Deux case de contracture hysteric, d'origine traumatique, Euvres Complet. Bur. Prog. Medical, Paris. 3 (n.d.) 97–124.
10. J. Bogousslavsky, S. Dieguez, Sigmund Freud and hysteria: The etiology of psychoanalysis?, Hysteria Rise an Enigm. 35 (2014) 109–125. doi:10.1159/000360244.
11. J. Stone, R. Hewett, A. Carson, C. Warlow, M. Sharpe, The 'disappearance'of hysteria: historical mystery or illusion?, J. R. Soc. Med. 101 (2008) 12–18.
12. S. Nettleton, I. Watt, L. O'Malley, P. Duffey, Understanding the narratives of people who live with medically unexplained illness, Patient.Educ.Couns. 56 (2005) 205–210.
13. J. Stone, What should we say to patients with symptoms unexplained by disease? The "number needed to offend," Bmj. 325 (2002) 1449–1450. doi:10.1136/bmj.325.7378.1449.
14. A.J. Carson, J. Stone, C. Warlow, M. Sharpe, Patients whom neurologists find difficult to help, J. Neurol. Neurosurg. Psychiatry. 75 (2004) 1776–1778.
15. R.W. Evans, R.E. Evans, A survey of neurologists on the likeability of headaches and other neurological disorders, Headache. 50 (2010) 1126–1129.
16. R. Kanaan, D. Armstrong, S. Wessely, Limits to truth-telling: neurologists' communication in conversion disorder, Patient.Educ.Couns. 77 (2009) 296–301.
17. A.J. Espay, L.M. Goldenhar, V. Voon, A. Schrag, N. Burton, A.E. Lang, Opinions and clinical practices related to diagnosing and managing patients with psychogenic movement disorders: An international survey of movement disorder society members, Mov. Disord. 24 (2009) 1366–1374. doi:10.1002/mds.22618.
18. J. Stone, Functional neurological disorders: The neurological assessment as treatment, Pract. Neurol. 16 (2016) 7–17. doi:10.1136/practneurol-2015-001241.
19. M.J. Edwards, Functional neurological symptoms: Welcome to the new normal, Pract. Neurol. 16 (2016) 2–3. doi:10.1136/practneurol-2015-001310.

20. J. Stone, The bare essentials: Functional symptoms in neurology., Pract. Neurol. 9 (2009) 179–189. doi:10.1136/jnnp.2009.177204.

21. M.J. Edwards, R.A. Adams, H. Brown, I. Parees, K.J. Friston, A Bayesian account of "hysteria," Brain. 135 (2012) 3495–3512.

22. K.J. Friston, C. Buechel, G.R. Fink, J. Morris, E. Rolls, R.J. Dolan, Psychophysiological and Modulatory Interactions in Neuroimaging, Neuroimage. 229 (1997) 218–229.

23. K. Carlsson, P. Petrovic, S. Skare, K.M. Petersson, M. Ingvar, Tickling expectations: neural processing in anticipation of a sensory stimulus., J. Cogn. Neurosci. 12 (2000) 691–703. doi:10.1162/089892900562318.

24. K. Friston, J. Kilner, L. Harrison, A free energy principle for the brain, J. Physiol. 100 (2006) 70–87. doi:10.1016/J.JPHYSPARIS.2006.10.001.

25. V. Voon, C. Brezing, C. Gallea, M. Hallett, Aberrant Supplementary Motor Complex and Limbic Activity During Motor Preparation in Motor Conversion Disorder, 26 (2011) 2396–2403. doi:10.1002/mds.23890.

26. P.D. van, T.A. Saifee, P. Schwingenschuh, P. Katschnig, K.P. Bhatia, M.A. Tijssen, M.J. Edwards, Attention to self in psychogenic tremor, Mov Disord. (2011).

27. I. Pareés, T.A. Saifee, P. Kassavetis, M. Kojovic, I. Rubio-Agusti, J.C. Rothwell, K.P. Bhatia, M.J. Edwards, Believing is perceiving: Mismatch between self-report and actigraphy in psychogenic tremor, Brain. 135 (2012) 117–123. doi:10.1093/brain/awr292.

28. S.M. Kranick, J.W. Moore, N. Yusuf, V.T. Martinez, K. Lafaver, M.J. Edwards, A.R. Mehta, P. Collins, N.A. Harrison, P. Haggard, M. Hallett, V. Voon, Action-Effect Binding Is Decreased in Motor Conversion Disorder : Implications for Sense of Agency, 00 (2013) 1–7. doi:10.1002/mds.25408.

29. M.J. Edwards, G. Moretto, P. Schwingenschuh, P. Katschnig, K.P. Bhatia, P. Haggard, Abnormal sense of intention preceding voluntary movement in patients with psychogenic tremor, Neuropsychologia. 49 (2011) 2791–2793. doi:10.1016/j.neuropsychologia.2011.05.021.

30. I. Pareés, H. Brown, A. Nuruki, R.A. Adams, M. Davare, K.P. Bhatia, K. Friston, M.J. Edwards, Loss of sensory attenuation in patients with functional (psychogenic) movement disorders, (2014) 2916–2921. doi:10.1093/brain/awu237.

31. S.M.A. Van Der Salm, M.A.J. Tijssen, J.H.T.M. Koelman, A. Van Rootselaar, The bereitschaftspotential in jerky movement disorders, (2012) 1162–1167. doi:10.1136/jnnp-2012-303081.

32. V. Voon, C. Gallea, N. Hattori, M. Bruno, V. Ekanayake, M. Hallett, The involuntary nature of conversion disorder, Neurology. 74 (2010) 223–228.

33. S. Aybek, T.R. Nicholson, F. Zelaya, O.G.O. Daly, T.J. Craig, A.S. David, R.A. Kanaan, Neural Correlates of Recall of Life Events in Conversion Disorder, (2014) 12–15. doi:10.1001/jamapsychiatry.2013.2842.

34. V. Voon, C. Brezing, C. Gallea, R. Ameli, K. Roelofs, W.C. Lafrance, M. Hallett, Emotional stimuli and motor conversion disorder, Brain. 133 (2010) 1526–1536. doi:10.1093/brain/awq054.

35. K. Czarnecki, D.T. Jones, M.S. Burnett, B. Mullan, J.Y. Matsumoto, SPECT perfusion patterns distinguish psychogenic from essential tremor, Park. Disord. 17 (2011) 328–332.

36. M. van Beilen, B.M. de Jong, E.W. Gieteling, R. Renken, K.L. Leenders, Abnormal parietal function in conversion paresis, PLoS One. 6 (2011). doi:10.1371/journal.pone.0025918.

37. Stepped care for functional neurological symptoms, (2012).

38. N.K. Sethi, J. Stone, M. Edwards, Trick or treat? Showing patients with functional (psychogenic) motor symptoms their physical signsAuthor Response, Neurology. 80 (2013) 869.

39. G. Nielsen, J. Stone, M.J. Edwards, Physiotherapy for functional (psychogenic) motor symptoms: A systematic review, J. Psychosom. Res. 75 (2013) 93–102. doi:10.1016/j.jpsychores.2013.05.006.

40. A.A. Jordbru, L.M. Smedstad, O. Klungsøyr, E.W. Martinsen, Psychogenic gait disorder: a randomized controlled trial of physical rehabilitation with one-year follow-up., J. Rehabil. Med. 46 (2014) 181–7. doi:10.2340/16501977-1246.

41. R. McCormack, J. Moriarty, J.D. Mellers, P. Shotbolt, R. Pastena, N. Landes, L. Goldstein, S. Fleminger, A.S. David, Specialist inpatient treatment for severe motor conversion disorder: a retrospective comparative study., J. Neurol. Neurosurg. Psychiatry. 85 (2014) 895–900. doi:10.1136/jnnp-2013-305716.

42. T.A. Saifee, P. Kassavetis, I. Pareés, M. Kojovic, L. Fisher, L. Morton, J. Foong, G. Price, E.M. Joyce, M.J. Edwards, Inpatient treatment of functional motor symptoms: A long-term follow-up study, J. Neurol. 259 (2012) 1958–1963. doi:10.1007/s00415-012-6530-6.

43. K. Czarnecki, J.M. Thompson, R. Seime, Y.E. Geda, J.R. Duffy, J.E. Ahlskog, Functional movement disorders: Successful treatment with a physical therapy rehabilitation protocol, Park. Relat. Disord. 18 (2012) 247–251. doi:10.1016/j.parkreldis.2011.10.011.

Part 1. Mechanism

Clinical aspects

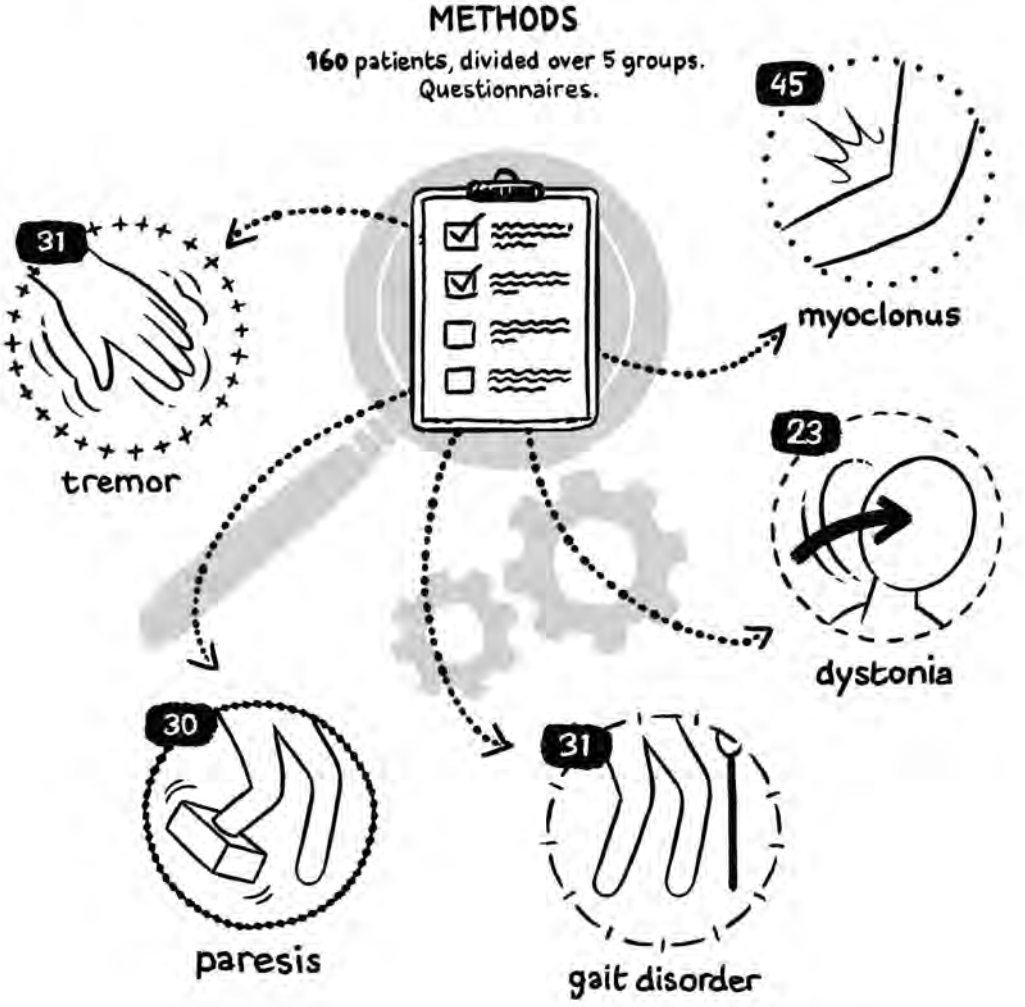
Chapter 1.

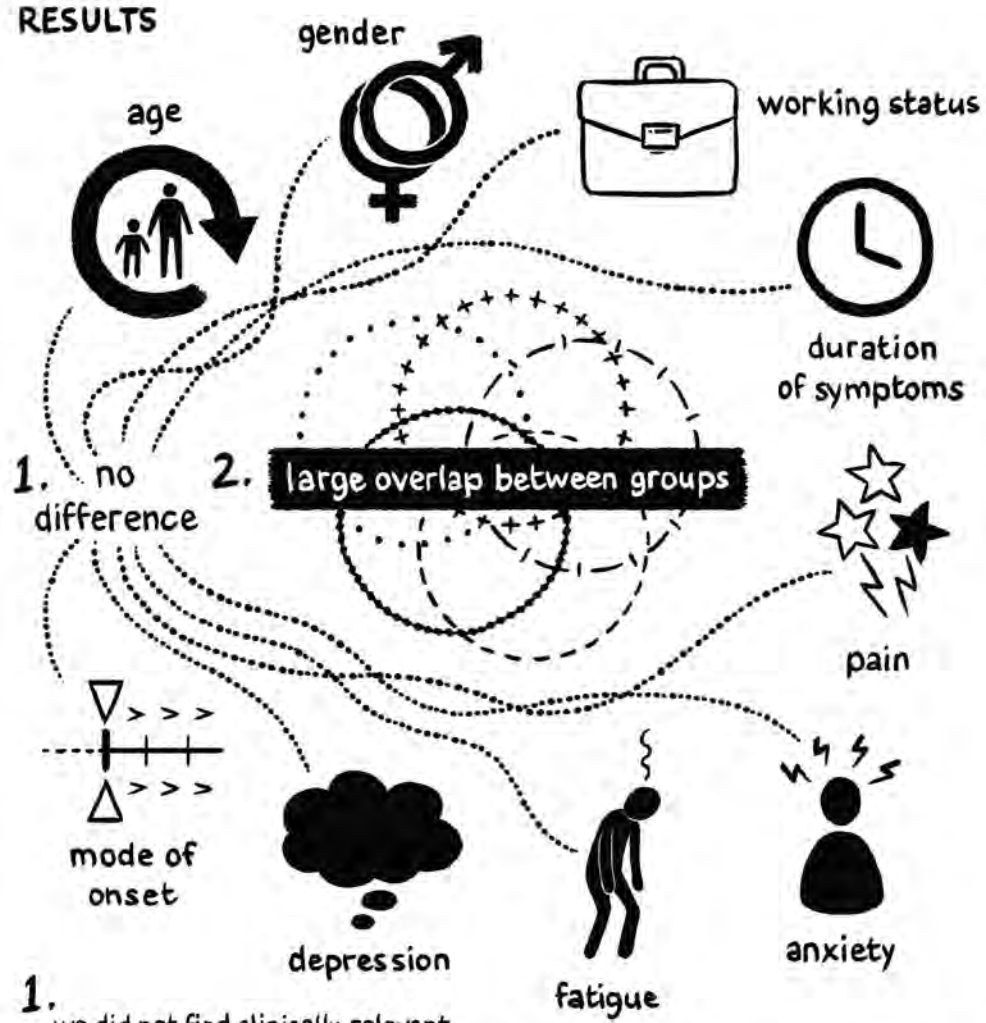
Shared demographics and comorbidities in different functional motor disorders.

Gelauff JM, Rosmalen JGM, Gardien J, Stone J, Tijssen MAJ

Accepted for publication in: Parkinson and related disorders, 2019

1. Do patients with different functional motor symptoms share demographics, co-morbid symptoms and quality of life?





1. we did not find clinically relevant differences between groups of functional motor symptoms, regarding demographics, triggers and non-motor features (depression, fatigue, anxiety, pain)

2. patients rated a large number of additional motor symptoms

this suggests a large overlap in phenotype and possibly underlying mechanisms of functional motor symptoms.

ABSTRACT

Introduction: Functional motor disorders are often delineated according to the dominant motor symptom. In a large cohort, we aimed to find if there were differences in demographics, mode of onset, pain, fatigue, depression and anxiety and levels of physical functioning, quality of life and social adjustment between patients with different dominant motor symptoms.

Methods: Baseline data from the Self-Help and Education on the Internet for Functional Motor Disorders Trial was used. Patients were divided into dominant motor symptom groups based on the diagnosis of the referring neurologist. Data on the above topics were collected by means of an online questionnaire and compared between groups using parametric and nonparametric statistics.

Results: In 160 patients a dominant motor symptom could be determined, 31 had tremor, 45 myoclonus, 23 dystonia, 30 paresis, 31 gait disorder. No statistical differences between groups were detected for demographics, mode of onset and severity of pain, fatigue, depression and anxiety. Physical functioning was worse in the gait disorder group (median 20, IQR 25) compared to tremor (50 (55), p=0.002) and myoclonus (50 (52), p=0.001). Work and social adjustment was less impaired in the myoclonus group (median 20, IQR 18) compared to gait disorder (median 30, IQR18, p<0.001) and paresis (28, IQR 10, p=0.001). Self-report showed large overlap in motor symptoms.

Conclusion: No differences were detected between groups of functional motor symptoms, regarding demographics, mode of onset, depression, anxiety, pain and fatigue. The large overlap in symptoms contributes to the hypothesis of shared underlying mechanisms of functional motor disorders.

INTRODUCTION

Functional motor disorders (FMD) consist of involuntary movements, posturing, gait disorder and paresis, that are internally inconsistent or incongruent with patterns of pathophysiological disease [1]. In organic movement disorders, detailed phenotyping of the motor symptoms is important to determine a phenomenological classification and to make an etiological diagnosis. This is increasingly expanded with motor phenotype specific associated non-motor features, like anxiety, depression, pain and fatigue and demographic differences [2–4]. It is unclear if these same associations exist in FMD.

FMDs are often delineated according to the dominant movement disorder such as tremor, dystonia or paresis. All FMD are assumed to share the same pathophysiological mechanism, but a shared mechanism cannot explain why one patient would suffer from paresis and another from tremor. It has been suggested based on clinical experience that specific FMDs are associated with for example gender, age at onset or pain. A small study in which functional paresis was compared to functional movement disorders has found relatively non-specific differences, like male predominance, lower psychiatric hospitalisation and higher incidence of head trauma in functional paresis [5]. When comparing patients with non-epileptic attacks to FMD, differences in risk factors, etiological background and psychological comorbidity were found [6] [7]. A review paper comparing non-epileptic attacks and FMD however, concluded that similarities exceed the differences in terms of demographics and associated psychological and physical symptoms [8]. From individual studies focussing on single FMD non-motor symptoms like depression, anxiety, fatigue and pain seem to be comparably high [9–13]. However, a direct comparison between groups has not been performed.

Here, we aimed to find if there were differences between different FMDs, by comparing demographics, mode of onset, non-motor symptoms pain, fatigue, depression and anxiety and levels of physical functioning, quality of life and social adjustment and self-rated additional motor symptoms between patients with different dominant motor symptoms, as categorised by the referring neurologist.

METHODS

Participants

All patients were included as part of a randomised Self-Help and Education on the Internet for Functional Motor Disorders Trial (SHIFT) (clinicaltrials.gov: NCT02589886). This was a two-group parallel superiority non-blinded randomised controlled trial in which patients were randomised to receive an education and self-help website or usual care. Patients were referred from 31 neurology centres across the Netherlands.

Between October 2015 and July 2017, patients considered eligible by the referring neurologist were contacted and informed by email or post. Inclusion in the SHIFT study required a functional motor disorder diagnosed by a neurologist, associated distress or impairment in social, occupational or other important areas of functioning, regular access to the internet, and Dutch language proficiency. Patients were excluded if they were unable to provide informed consent due to cognitive problems and if they were under 18 years of age. All included patients provided written informed consent. Patients with co-morbid neurological disease were not excluded from the study, but were told that this intervention was aimed at their functional motor symptoms.

Data for the current study came from the baseline questionnaires for this trial gathered before randomization took place. We previously published an article on the high prevalence of fatigue, from this same baseline data [14]. Data for the SHIFT study was collected in accordance with the ethical and legal guidelines of the University Medical Center Groningen (Medical Ethical Committee reference number: METc 2015/141, M14.150920).

Determination of the dominant motor symptom

Categorisation of patients into groups of the dominant motor symptom was based on the neurologist rating of the motor symptoms. The dominant motor symptom for each patient was determined based on the diagnosis of the referring neurologist, either provided directly on request, or via their clinic letter. When the neurologist was unable to identify one dominant motor symptom but rather thought two or more symptoms were equally severe (and/or impairing) or when referring information could not be obtained (neurologists could not be contacted/referring letters were not available/patients did not consent to obtain this information), the dominant motor symptom was labeled ' unknown' and these patients were left out of the group comparisons.

Demographics and onset of symptoms.

Patients filled out questionnaires online including their age and sex. A multiple choice question was used asking in how much time the motor symptoms had arisen, with the following options: within seconds to minutes, minutes to 6 hours, more than 6 hours, symptoms were present at awakening or after an operation. Furthermore, patients were asked if migraine, a panic attack, general anesthesia, illness due to an infection, medication side effects, sleep paralysis, a pain, fatigue, or injury preceded onset of the first motor symptom(s), or if symptoms were first noticed by a health care professional.

Pain, Fatigue, Depression and Anxiety

With regard to non-motor features, we assessed pain using the pain subscale of the RAND36 (the health-related quality of life questionnaire which is almost identical to the Short-Form 36 questionnaire, (maximum score is 100 which stands for low pain) [15], fatigue using the subdomain fatigue severity of the Checklist Individual Strength (CIS, 8-56) [16], depressive symptoms using the Patient Health Questionnaire 9 (PHQ-9; 0-27) [17]and anxiety measured using the Generalized Anxiety Disorder Questionnaire (GAD-7; 0-14) [18].

Physical Functioning, Quality of Life, Occupational and Social Functioning

Physical functioning was measured with the corresponding subscale of the RAND36 (0-100, with 100 reflecting optimal functioning). Quality of life was measured with a single question from the WHO-QoL questionnaire: "How would you rate your quality of life on a 5-point Likert scale" [19]. Work and social adjustment were assessed using the Work and Social Adjustment Scale (score range 0-40, with 0 reflecting best adjustment) [20]. Patients were also asked to report their working status and whether they received benefits for health-related reasons by means of several multiple-choice questions.

Patient-rated motor symptoms

We asked patients to indicate the presence and severity of the functional motor symptoms they experience using a variety of descriptors, specifically tremor (tremor/trembling/shivering), myoclonus (myoclonus/jerky movements), dystonia (dystonia/abnormal posturing), paresis (paresis/weakness/loss of strength) and gait disorder. All patients rated each of these five functional motor symptoms. They were were asked to rate the severity of each symptom on a 7-point Likert scale (0= not present – 7 = very severe), conform the change in presenting symptoms scale baseline measurement (CPS).

Statistical analyses

For group comparisons, ANOVA was used for normally distributed data and Kruskall Wallis tests for non-normally distributed and ordinal data. Chi squared tests were used to compare categorical variables. When statistical differences between groups were found with a p-value < 0.05, Mann-Whitney U tests were used for pairwise comparisons between groups. SPSS by IBM version 23 was used to perform statistical analyses. Correction for multiple comparisons according to Bonferroni was performed and resulted in a threshold p-value of 0.003.

To assess differences in prevalence of additional motor symptoms between dominant motor symptom groups, Chi squared tests were used. Correlations were made using Spearman's rho non-parametric analyses.

The patient-rated severity of the main motor symptom was compared to patient-rated severity of the other motor symptoms by a Friedman test.

RESULTS

Of the 186 patients that were included in the SHIFT study, 31 had tremor, 45 myoclonus, 23 dystonia, 30 paresis, 31 gait disorder, 3 facial dystonia as the dominant motor symptom recorded by the neurologist and for 23 cases, classification according to their dominant motor symptom was not possible because the referring neurologists could not be contacted (n=19) or he/she considered two or more motor symptoms to be comparably prominent (n=4). Cases with facial dystonia (n=3) were not included in the between group analyses, given their low prevalence.

Demographics and motor symptom characteristics

Mean age of the overall cohort (n=186) was 48 years (SD 15); females formed a large majority (71%). The median duration of symptoms was 24 months (IQR 6-69). Symptom onset was acute (within minutes) in 40% (n=74) of cases. There were no significant differences between groups in terms of age, sex, symptom duration, onset duration or mode of onset. Reported mode and clinical features at onset were equally distributed in all five dominant motor symptom groups with no statistical differences between groups. In the total group the commonest factors at onset were pain (n=46, 26%), noticed by a health care professional (n=18, 10%), injury (n=15,8%) and general anesthesia (n=14, 8%) (Table 2).

Dominant functional motor symptom	Total	Tremor	Myoclonus	Dystonia	Paresis	Gait disorder	Group comparison
N	186	31	45	23	30	31	-
Demographics and symptoms							
Age in years (mean, SD, min-max)	48 (15, 18-78)	55 (16, 21-78))	49 (17, 20-73)	44 (13, 18-65)	45 (14, 19-67)	51 (11, 20-69)	F = 2.5, p = 0.017[A]
Sex (n,%female)	132 (71%)	19 (61%)	33(73%)	15(65%)	24 (80%)	23(74%)	Chi^2 = 4.0, p = 0.406[C]
Duration of motor symptoms in months, median (IQR)	24 (6-69)	21 (5-69)	25 (9-104)	36 (18-154)	18 (3-50)	21 (11-73)	Chi^2 =5.5, p = 0.238[A]
Mode of Onset	74 (40%)	14 (45%)	20 (44%)	7 (30%)	11 (37%)	9 (29%)	Chi^2= 4.5
Within minutes	16 (9%)	3 (10%)	4 (9%)	1 (4%)	7 (23%)	-	p = 0.345[A]
Minutes-6 hours	60 (32%)	10 (32%)	13 (29%)	9 (39%)	3 (10%)	15 (49%)	
> 6 hours	27 (14%)	4 (13%)	5 (11%)	4 (17%)	6 (20%)	6 (19%)	
At waking up	9 (5%)	-	3 (7%)	2 (9%)	3 (10%)	1 (3%)	
After general anaesthesia							
Any other functional motor symptom	161 (87%)	27 (87%)	35 (77%)	23 (100%)	27 (90%)	28 (90%)	Chi^2=8.1, p=0.088[A]
Self-rated additional motor	-	-	22 (49%)	11 (48%)	12 (40%)	12 (39%)	$Chi^{2=}$ 4.4,
symptoms (% severity ≥2 on CPS)	-	21 (68%)	-	8 (35%)	7 (23%)	10 (32%)	p=0.357[A]
Tremor	-	6 (20%)	13 (29%)	-	11 (37%)	15 (48%)	
Myoclonus	-	10 (33%)	15 (33%)	14 (61%)	-	20 (65%)	
Dystonia	-	7 (23%)	14 (31%)	11 (48%)	20 (67%)	-	
Paresis							
Gait disorder							
Pain (RAND36, range 0-100), median (IQR)	46 (22-80)	67 (22-100)	57 (40-95)	47 (22-78)	45 (22-60)	45 (22-78)	Chi^2= 7.8 p = 0.100[A]
Fatigue (CIS range 8-56), median (IQR) [#]	44 (35-44)	42 (35-53)	40 (32-52)	37 (20-51)	48 (42-54)	49 (38-54)	Chi^2= 9.7 p = 0.045[A]
Depression (PHQ-9, range 0-27), median (IQR) [#]	8 (4-13)	7 (4-14)	6 (3-14)	6 (1-9)	10 (6-15)	8 (5-13)	Chi^2= 8.7 p = 0.069[A]

Anxiety (GAD-7, range 0-14), median (IQR)	5 (0-9)	4 (0-9)	6 (0-9)	3 (0-8)	4 (0-10)	6 (0-9)	Chi^2= 1.1 p = 0.899 [A]
Physical Functioning, Quality of Life, Occupational and Social Impairment							
Physical functioning (RAND36) median (IQR)	**40 (20-65)**	**50 (25-80)**	**50 (25-78)**	**25 (10-70)**	**38 (15-50)**	**20 (15-40)**	**Chi^2= 16.0 p = 0.003** [A]
Quality of life (WHO-QoL, range 1-5), median (IQR)	3 (2-4)	3 (2-4)	3 (3-4)	3 (2-4)	3 (2-3)	3 (2-4)	Chi^2= 2.7 p = 0.615 [A]
In work/Studying	48 (26%)	7 (22,5%)	17 (38%)	6 (26%)	8 (27%)	2 (6%)	Chi^2= 12.7 p = 0.013 [A]
Not in work							
for non-medical reasons	34 (18%)	7 (22,5%)	11 (24%)	2 (9%)	3 (10%)	8 (26%)	
on benefits ⩽ 2 years	35 (19%)	4 (13%)	8 (18%)	3 (13%)	7 (23%)	7 (23%)	
on benefits > 2 years	69 (37%)	13 (42%)	9 (20%)	12 (52%)	12 (40%)	14 (45%)	
Work and social adjustment (WSAS, range 0-40) median (IQR)	**26 (16-32)**	**21 (13-32)**	**20 (9-27)**	**21 (16-30)**	**28 (24-34)**	**30 (26-34)**	**Chi^2= 21.8 p <0.001** [A]

Table 1. Comparison of dominant motor symptom groups. Median and IQR are given unless otherwise specified. Statistical testing: ANOVA([A]) Chi square ([C])and Kruskall Wallis([K]) and Kruskall Wallis(K) judged significant at the Bonferroni threshold of 0.003.. Nonclassified cases (n=23) and facial dystonia cases (n=3) were not included in the group comparison. #Missing: data on fatigue in 3 patients, data on depression in 2 patients.

Clinical features at onset	Total (n=179)	Tremor (n=29)	Myoclonus (n=42)	Dystonia (n=23)	Paresis (n=30)	Gait disorder (n=29)	Group comparison
Pain	46 (26%)	6 (21%)	8 (19%)	10 (44%)	8 (27%)	9 (29%)	Chi^2 5.3, P=0.255
Panic	8 (5%)	2 (7%)	1 (2%)	1 (4%)	3 (10%)	1 (3%)	Chi^2 4.4, P=0.348
Injury	15 (8%)	1 (3%)	3 (7%)	4 (17%)	3 (10%)	3 (10%)	Chi^2 3.3, P=0.514
General aneasthesia	14 (8%)	2 (7%)	5 (12%)	2 (9%)	4 (14%)	1 (3%)	Chi^2 2.3, P=0.678
Medication	6 (3%)	1 (3%)	1 (2%)	1 (4%)	1 (3%)	1 (3%)	Chi^2 0.2, P=0.996
Sleep paralysis	4 (2%)	-	-	-	2 (7%)	1 (3%)	Chi^2 5.6, P=0.228
Infection	8 (5%)	1 (3%)	2 (5%)	1 (4%)	1 (3%)	2 (7%)	Chi^2 0.6, P=0.968
Migraine	3 (2%)	2 (7%)	-	1 (4%)	1 (3%)	-	Chi^2 3.9, P=0.419
First noticed by health care professional	18 (10%)	2 (7%)	4 (10%)	4 (17%)	4 (13%)	2 (7%)	Chi^2 2.3, P=0.689

Table 2. Prevalence of clinical features at onset. More than one answer possible. *data missing: for 2 patients from the tremor group, 3 patients from the myoclonus group and 2 patients from the gait disorders group. Nonclassified cases (n=23) and facial dystonia patients (n=3) were not included in the group comparison.

Pain, Fatigue, Depression and Anxiety

Scores were high for pain and fatigue in the entire cohort (Table 1); pain median 46 (IQR 22-80) and fatigue median 44 (IQR 25-44). The median scores of depressive and anxiety symptoms were respectively 8 (IQR 4-13) out of a maximum score of 27 on the PHQ9 and 5 (IQR 0-9) of 14 on the GAD7. There were no statistically significant differences in the levels of pain, depression and anxiety between the dominant motor symptom groups. Differences in fatigue scores between groups did not remain significant after correction for multiple comparisons.

Physical Functioning, Quality of Life, Occupational and Social Functioning

Physical functioning (median 40 (IQR 20-65, score maximum 100)) and quality of life scores (median 3 out of 5 (IQR 2-4) were low in a majority of patients. The work and social adjustment score represents high impairment (26, (IQR 16-32), score maximum 40) and 56% (n=104) of patients were (temporarily or permanently) not in work and received benefits. Scores on physical functioning and work and social adjustment were different between groups. Pairwise comparisons showed that the gait disorder group had significantly worse physical functioning (median 20, IQR 15-40) than the tremor (50 (25-80), p=0.002) and myoclonus (50 (25-78), p=0.001) groups. The work and social adjustment scale was significantly more impaired in the gait disorder and paresis group compared to myoclonus (gait disorder: median 30 (IQR 26-34), versus myoclonus 20 (9-27), p<0.001, paresis 28 (24-34) versus myoclonus, p=0.001). There were no statistically significant differences between groups in quality of life scores, or in percentages of patients in work or receiving benefits for health-related reasons.

Patient-rated motor symptom severity

The severity of the dominant motor symptom on a scale from 0-7 (0 corresponding to total absence of the symptom, 7 corresponding to most severe) in each group was: Tremor median 4 (IQR3-5) (61% of patients had marked (5), severe (6) or very severe (7) symptoms), Myoclonus median 3 (IQR 2-4) (44% marked-very severe), dystonia median 3 (IQR 2-6) (43% marked-very severe), paresis median 3 (IQR 1-4) (47% marked-very severe), Gait disorder median 4 (IQR 3-5) (61% marked-very severe). The dominant motor symptom (as indicated by the neurologist) was self-rated as the most severe motor symptom in all groups (Friedman test for every group p<0.001) when compared to other motor symptoms that patients reported. Only in the dystonia group, paresis severity (median 3, IQR 0-5) was reported as high as dystonia severity (median 3, IQR 2-6) (Chi^2 = 14, Friedman test p=0.008).

There was a high prevalence of self-rated additional functional motor symptoms in all dominant motor symptom groups (77% (n=35) in the myoclonus group to 100% in the dystonia group, 87% (n=161) overall, Chi^2 7.0, p=0.134) , when counting all symptoms with a severity of 2 ('mildly bothered') or higher. Table 1 shows these additional patient-rated motor symptoms per dominant motor group. Overall, the median number of motor symptoms, including the dominant motor symptom, was 2 (IQR 2-4), with no statistically significant differences between dominant motor symptom groups (Chi^2 4.4, p=0.357).

DISCUSSION

In this study, we did not find differences in demographics, mode of onset, non-motor features, levels of physical disability or quality of life between patients with different types of functional motor symptoms. We found equally high rates of fatigue, pain, depression and anxiety in all dominant motor groups. We had expected that some symptoms, particular functional dystonia, might be associated with more pain [21,22]. However, patients with functional paresis or gait disorder as a dominant motor symptom had more severe impairment of physical functioning. Self-reported overlap in motor symptoms was high in all groups.

Tremor and myoclonus were overrepresented in our data compared to general neurology clinics [23,24], probably due a large number of referrals from movement disorders clinics rather than general neurology clinics in our data. In line with studies in this field, patients were mainly female, had a long symptom duration and were on average middle-aged. In 8% of our cohort, patients suffered some form of injury before symptom onset. This is lower than previously reported (10-37%), and would contradict the theory that the type of trigger might determine the motor phenotype in FMD. However, it is not clear to what extent the questionnaire used in this study can accurately assess triggering events as compared to the previously used interviews [25–27]. The speed of symptom onset was within minutes in 40% and within 6 hours in 49%, in line with findings in the literature, in which 54% of patients with movement disorders [25] and 49% of patients with paresis [26] had an acute onset. Acute onset in organic tremor, myoclonus and dystonia is rare and therefore could be a supportive diagnostic sign.

We did not find correlations between non-motor features fatigue, pain, depression and anxiety and groups of dominant motor symptoms. The high pain and fatigue

scores in all groups underline the growing realisation that non-motor symptoms are relevant in both functional and organic movement disorders and should be recognised when treatment strategies are chosen [14]. The lack of differences between groups stresses the importance of addressing non-motor features in all FMD patients. There are varying reports of psychopathology in functional motor symptoms. In the largest study into functional paresis (n=107) scores on pain and fatigue (median 33 (IQR 22) and 30 (35) of the SF36 scale respectively) and psychopathology (any current affective 61%, generalised anxiety in 21% of cases) were high [13]. It is possible that the frequency of depression and anxiety is higher than it appears in the data. Patients with FMD have been found to report lower rates in questionnaires than when questioned directly , because of stigma of mental illness and/or because of alexithymia [13,28]. We did not confirm small studies in which psychopathology seems less frequent in functional tremor and myoclonus [12,29].

Physical functioning and work and social activities were highly impaired in most patients and worse in paresis and gait disorders who are more likely to have persistent symptoms and problems walking than for example patients with tremor or myoclonus which is intermittent and doesn't affect ambulation. For the entire cohort, data relating to physical functioning, not being in work due to ill health and scores on the work and social adjustment scale, were comparable to the data in the literature [13,30,31].

This large overlap between patient-reported symptoms is an important finding. The current literature shows variable overlap in motor symptoms ranging from only 8% to 72% of patients with paresis reporting an additional motor symptom [9,13,32], and up to 79% of patients with a functional movement disorder that had another motor symptom [33]. The high rate in our study could be explained by the fact that we explicitly asked for severity of all motor symptoms within our questionnaire. Self-report could have led to an overestimation, compared to findings in neurological examination (at one timepoint), although for a disorder in which subjective report is arguably the key feature of the disorder [34], it is a valid method of assessment. Also, there was concordance between patients and neurologists when indicating the dominant motor symptom, which lends some weight to our exploratory analysis of motor symptom overlap.

There are several possible explanations for the lack of differences between groups. Similar rates of non-motor features, comparable demographics and the fact that we did not find an association between typical patterns of mode of onset

and motor phenotypes, might indicate a (at least partly) shared pathophysiological mechanism between the different motor symptoms. The large overlap between groups in terms of self-rated additional motor symptoms adds to that argument. Authors have highlighted the similarities between the broader group of functional syndromes, like sex ratios, comorbid emotional disorders and etiological factors and a comparable response to similar treatments across studies [35], which would be supported by the findings in our sample. Another explanation could be the potential difficulty physicians face when phenotyping functional motor disorders, because they are by definition clinically incongruent with recognized neurological disease. Myoclonus and tremor appear most linked, as we noticed that these terms were often used interchangeably in the history, examination and conclusion sections in the referral letters. However, the concordance between patients and neurologists when indicating the dominant motor symptom, affirms the existence of distinct dominant motor phenotypes.

Our data do not indicate specific treatment targets for the non-motor features in different motor symptom groups. Thus far, treatment that has been found effective for FMD is either symptom focused, like in physiotherapy [32], or a combination of elements generic to shared disability and symptoms (e.g. rehabilitation advice), symptom specific elements and/or individual elements (e.g. in psychotherapy) [36–38]. It therefore seems optimal to combine specific symptom-tailored with a recognition of the likelihood of shared comorbidities. Measuring outcome in FMD is subject of debate. Our data show that motor symptoms are not distinctive for non-motor profiles or general outcome. Therefore they support the notion that with respect to FMD, it may not be necessary to focus excessively on motor symptom phenomenology to categorise and measure outcome in FMD. This approach has also been adopted by the 'Simplified Functional Movement Disorders Scale' for example [39].

Our study has several limitations. Differences between groups might have been missed due to the relatively small size of the groups or due to co-morbid neurological disease that might have been present in some cases. The results might be partly skewed by recall bias or due to the fact that we cannot be sure the online questionnaires were always filled out by the patients themselves. As discussed above, self-report has disadvantages. Especially the fact that motor symptom severity in this study was rated by patients themselves should be taken into account when interpreting the data.

CONCLUSION

In this study we did not find clinically relevant differences between groups of functional motor symptoms, regarding demographics, triggers and non-motor features such as depression, anxiety, pain and fatigue. Also, patients rated a large number of additional motor symptoms, apart from the dominant motor symptom as reported by the neurologist. This suggests a large overlap in phenotype and possibly underlying mechanisms of functional motor symptoms. High pain and fatigue scores in all groups underline the growing evidence that non-motor symptoms are relevant in both functional and organic movement disorders and should be recognised when planning treatment strategies.

REFERENCES

1. A. Lehn, J. Gelauff, I. Hoeritzauer, L. Ludwig, L. McWhirter, S. Williams, P. Gardiner, A. Carson, J. Stone, Functional neurological disorders: mechanisms and treatment, J. Neurol. 263 (2016) 611–620. doi:10.1007/s00415-015-7893-2.
2. B. Müller, J. Assmus, K. Herlofson, J.P. Larsen, O.B. Tysnes, Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease, Park. Relat. Disord. 19 (2013) 1027–1032. doi:10.1016/j.parkreldis.2013.07.010.
3. M. Smit, A.S.J. Kamphuis, A.L. Bartels, V. Han, R.E. Stewart, I. Zijdewind, M.A. Tijssen, Fatigue, Sleep Disturbances, and Their Influence on Quality of Life in Cervical Dystonia Patients, Mov. Disord. Clin. Pract. 4 (2017) 517–523. doi:10.1002/mdc3.12459.
4. E.R. Timmers, A. Kuiper, M. Smit, A.L. Bartels, D.J. Kamphuis, N.I. Wolf, B.T. Poll-The, T. Wassenberg, E.A.J. Peeters, T.J. de Koning, M.A.J. Tijssen, Non-motor symptoms and quality of life in dopa-responsive dystonia patients, Park. Relat. Disord. 45 (2017) 57–62. doi:10.1016/j.parkreldis.2017.10.005.
5. N. Matin, S.S. Young, B. Williams, W.C. LaFrance, J.N. King, D. Caplan, Z. Chemali, J.B. Weilburg, B.C. Dickerson, D.L. Perez, Neuropsychiatric Associations With Gender, Illness Duration, Work Disability, and Motor Subtype in a U.S. Functional Neurological Disorders Clinic Population, J. Neuropsychiatry Clin. Neurosci. 29 (2017) 375–382. doi:10.1176/appi.neuropsych.16110302.
6. R.A.A. Kanaan, R. Duncan, L.H. Goldstein, J. Jankovic, A.E. Cavanna, Are psychogenic non-epileptic seizures just another symptom of conversion disorder?, J. Neurol. Neurosurg. Psychiatry. 88 (2017) 425–429. doi:10.1136/jnnp-2017-315639.
7. V. Ekanayake, S. Kranick, K. LaFaver, A. Naz, A. Frank Webb, W.C. LaFrance, M. Hallett, V. Voon, Personality traits in psychogenic nonepileptic seizures (PNES) and psychogenic movement disorder (PMD): Neuroticism and perfectionism, J. Psychosom. Res. 97 (2017) 23–29. doi:10.1016/j.jpsychores.2017.03.018.
8. R. Erro, F. Brigo, E. Trinka, G. Turri, M.J. Edwards, M. Tinazzi, Psychogenic nonepileptic seizures and movement disorders: A comparative review, Neurol. Clin. Pract. 6 (2016) 138–149. doi:10.1212/CPJ.0000000000000235.
9. A. Schrag, M. Trimble, N. Quinn, K. Bhatia, The syndrome of fixed dystonia: An evaluation of 103 patients, Brain. 127 (2004) 2360–2372. doi:10.1093/brain/awh262.
10. I.N. Petrović, A. Tomić, M.M. Vončina, D. Pešić, V.S. Kostić, Characteristics of two distinct clinical phenotypes of functional (psychogenic) dystonia: follow-up study, J. Neurol. 265 (2018) 82–88. doi:10.1007/s00415-017-8667-9.
11. A. Tomić, I. Petrović, D. Pešić, M.M. Vončina, M. Svetel, N.D. Mišković, A. Potrebić, D.L. Toševski, V.S. Kostić, Is there a specific psychiatric background or personality profile in functional dystonia?, J. Psychosom. Res. 97 (2017) 58–62. doi:10.1016/j.jpsychores.2017.04.004.
12. R. Zutt, J.M. Gelauff, M. Smit, J.C. van Zijl, J. Stone, M.A.J. Tijssen, The presence of depression and anxiety do not distinguish between functional jerks and cortical myoclonus, Park. Relat. Disord. 45 (2017) 90–93. doi:10.1016/j.parkreldis.2017.09.023.
13. J. Stone, C. Warlow, M. Sharpe, The symptom of functional weakness: A controlled study of 107 patients, Brain. 133 (2010) 1537–1551. doi:10.1093/brain/awq068.
14. J.M. Gelauff, E.M. Kingma, J.S. Kalkman, R. Bezemer, B.G.M. van Engelen, J. Stone, M.A.J. Tijssen, J.G.M. Rosmalen, Fatigue, not self-rated motor symptom severity, affects quality of life in functional motor disorders, J. Neurol. 265 (2018) 1803–1809. doi:10.1007/s00415-018-8915-7.
15. C. Jenkinson, A. Coulter, L. Wright, Short form 36 (SF36) health survey questionnaire: normative data for adults of working age, BMJ. 306 (1993) 1437–1440.

16. M. Worm-smeitink, M. Gielissen, L. Bloot, H.W.M. Van Laarhoven, B.G.M. Van Engelen, The assessment of fatigue : Psychometric qualities and norms for the Checklist individual strength, J. Psychosom. Res. 98 (2017) 40–46. doi:10.1016/j.jpsychores.2017.05.007.

17. K. Kroenke, R.L. Spitzer, J.B.W. Williams, The PHQ-9, J Gen Intern Med. 16 (2001) 606–613.

18. B. Löwe, O. Decker, S. Müller, E. Brähler, D. Schellberg, W. Herzog, P.Y. Herzberg, Validation and Standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population, Med. Care. 46 (2008) 266–274. doi:10.1097/MLR.0b013e318160d093.

19. T.H.E.W. Group, Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment, (1998) 551–558.

20. G. Pedersen, E.H. Kvarstein, T. Wilberg, The Work and Social Adjustment Scale: Psychometric properties and validity among males and females, and outpatients with and without personality disorders, Personal. Ment. Health. 11 (2017) 215–228. doi:10.1002/pmh.1382.

21. N.M. Ibrahim, D. Martino, B.P.C. Van De Warrenburg, N.P. Quinn, K.P. Bhatia, R.J. Brown, M. Trimble, A. Schrag, Parkinsonism and Related Disorders The prognosis of fixed dystonia : A follow-up study, 15 (2009) 592–597. doi:10.1016/j.parkreldis.2009.02.010.

22. A. Schrag, M. Trimble, N. Quinn, K. Bhatia, The syndrome of fixed dystonia: an evaluation of 103 patients, Brain. 127 (2004) 2360–2372.

23. J. Stone, A. Carson, R. Duncan, R. Roberts, C. Warlow, C. Hibberd, R. Coleman, R. Cull, G. Murray, A. Pelosi, J. Cavanagh, K. Matthews, R. Goldbeck, R. Smyth, J. Walker, M. Sharpe, Who is referred to neurology clinics?--the diagnoses made in 3781 new patients, Clin.Neurol.Neurosurg. 112 (2010) 747–751.

24. O. Ahmad, K.E. Ahmad, Functional neurological disorders in outpatient practice: An Australian cohort, J. Clin. Neurosci. 28 (2016) 93–96. doi:10.1016/j.jocn.2015.11.020.

25. I. Pareés, M. Kojovic, C. Pires, I. Rubio-Agusti, T.A. Saifee, A. Sadnicka, P. Kassavetis, A. MacErollo, K.P. Bhatia, A. Carson, J. Stone, M.J. Edwards, Physical precipitating factors in functional movement disorders, J. Neurol. Sci. 338 (2014) 174–177. doi:10.1016/j.jns.2013.12.046.

26. J. Stone, C. Warlow, M. Sharpe, Functional weakness: Clues to mechanism from the nature of onset, J. Neurol. Neurosurg. Psychiatry. 83 (2012) 67–69. doi:10.1136/jnnp-2011-300125.

27. J. Stone, A. Carson, H. Aditya, R. Prescott, M. Zaubi, C. Warlow, M. Sharpe, The role of physical injury in motor and sensory conversion symptoms: a systematic and narrative review, J.Psychosom.Res. 66 (2009) 383–390.

28. R. Jalilianhasanpour, B. Williams, I. Gilman, M.J. Burke, S. Glass, G.L. Fricchione, M.S. Keshavan, W.C. Lafance, D.L. Perez, Affective Symptoms in Motor Functional Neurological Disorders, J Psychosom Res. 107 (2018) 55–61. doi:10.1016/j.jpsychores.2018.02.005.Resilience.

29. G. Deuschl, B. Köster, C.H. Lucking, C. Scheidt, Diagnostic and pathophysiological aspects of psychogenic tremors, Mov. Disord. 13 (1998) 294–302. doi:10.1002/mds.870130216.

30. A. Carson, J. Stone, C. Hibberd, G. Murray, R. Duncan, R. Coleman, C. Warlow, R. Roberts, A. Pelosi, J. Cavanagh, K. Matthews, R. Goldbeck, C. Hansen, M. Sharpe, Disability, distress and unemployment in neurology outpatients with symptoms "unexplained by organic disease," J. Neurol. Neurosurg. Psychiatry. 82 (2011) 810–813. doi:10.1136/jnnp.2010.220640.

31. A. Carson, A. Lehn, Epidemiology, Handb. Clin. Neurol. 139 (2016) 47–60. doi:10.1016/B978-0-12-801772-2.00005-9.
32. G. Nielsen, M. Buszewicz, F. Stevenson, R. Hunter, K. Holt, M. Dudziec, L. Ricciardi, J. Marsden, E. Joyce, M. Edwards, Randomised feasibility study of physiotherapy for patients with functional motor symptoms, J. Neurol. Neurosurg. Psychiatry. 88 (2017) 484–490. doi:10.1136/jnnp-2016-314408.
33. D.T. Williams, B. Ford, S. Fahn, Phenomenology and psychopathology related to psychogenic movement disorders., Adv. Neurol. 65 (1995) 231–257.
34. I. Pareés, T.A. Saifee, P. Kassavetis, M. Kojovic, I. Rubio-Agusti, J.C. Rothwell, K.P. Bhatia, M.J. Edwards, Believing is perceiving: Mismatch between self-report and actigraphy in psychogenic tremor, Brain. 135 (2012) 117–123. doi:10.1093/brain/awr292.
35. S. Wessely, C. Nimnuan, M. Sharpe, Functional somatic syndromes: one or many? [see comments], Lancet. 354 (1999) 936–939. doi:10.1016/S0140-6736(98)08320-2.
36. A.A. Jordbru, L.M. Smedstad, O. Klungsøyr, E.W. Martinsen, Psychogenic gait disorder: a randomized controlled trial of physical rehabilitation with one-year follow-up., J. Rehabil. Med. 46 (2014) 181–7. doi:10.2340/16501977-1246.
37. C. Dallocchio, M. Tinazzi, F. Bombieri, N. Arnó, R. Erro, Cognitive Behavioural Therapy and Adjunctive Physical Activity for Functional Movement Disorders (Conversion Disorder): A Pilot, Single-Blinded, Randomized Study, Psychother. Psychosom. 85 (2016) 381–383. doi:10.1159/000446660.
38. K. Czarnecki, J.M. Thompson, R. Seime, Y.E. Geda, J.R. Duffy, J.E. Ahlskog, Functional movement disorders: Successful treatment with a physical therapy rehabilitation protocol, Park. Relat. Disord. 18 (2012) 247–251. doi:10.1016/j.parkreldis.2011.10.011.
39. G. Nielsen, L. Ricciardi, A.M. Meppelink, K. Holt, CLINICAL PRACTICE A Simplified Version of the Psychogenic Movement Disorders Rating Scale : The Simplified Functional Movement Disorders Rating Scale (S-FMDRS), Mov. Disord. Clin. Pract. (2017) 1–7. doi:10.1002/mdc3.12475.

Authors' Roles

JG participated in conception, organization, execution of the research project, design and execution of statistical analysis and wrote the first draft.

JR participated in the conception and design of the study, the design of the statistical methods and reviewed the results and the manuscript.

JG participated in conception, organization and execution of the research project and helped writing the first draft.

JS reviewed and critiqued the statistical analysis and the manuscript

MT participated in the conception and design of the study, the organization and execution of the project and reviewed the results and the manuscript.

Chapter 2.

Fatigue, not self-rated motor symptom severity, affects quality of life in functional motor disorders.

Gelauff JM, Kingma EM, Kalkman JS, Bezemer R, van Engelen BGM, Stone J, Tijssen MAJ, Rosmalen JGM

Article published in Journal of Neurology 2018 doi: 10.1007/s00415-018-8915-7

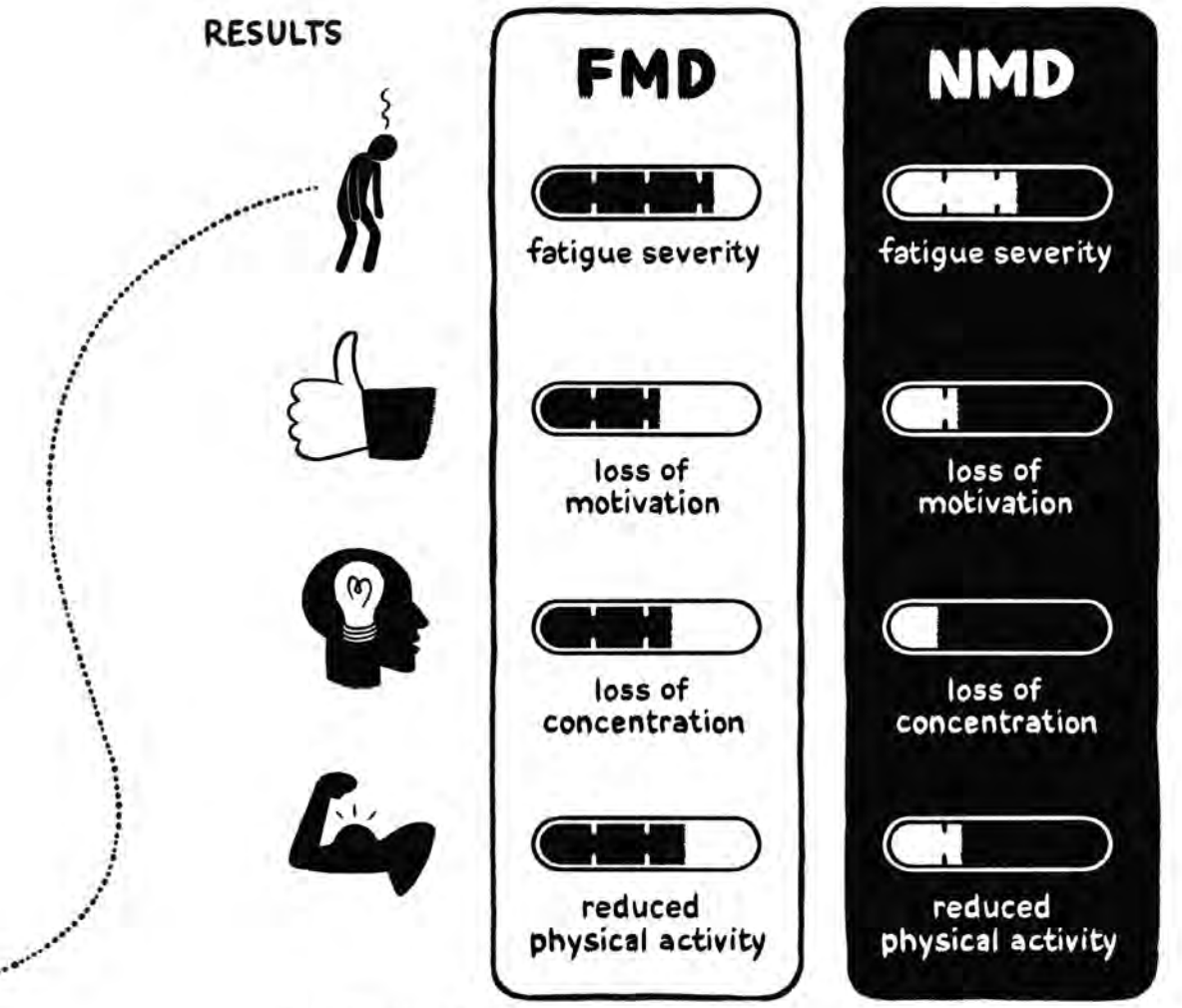
2. How severe is fatigue in functional motor disorders and does it influence quality of life?

METHODS

Checklist Individual Strength (CIS) questionnaire
in **181** patients with functional motor disorders (FMD) compared to
a group of **217** patients with neuromuscular disorders (NMD)

Fatigue severity
significantly affected
quality of life and
self-rated health

RESULTS



Fatigue was found to be a prevalent and impairing problem in patients with a functional motor disorder.

ABSTRACT

While fatigue is found to be an impairing symptom in functional motor disorders (FMD) in clinical practice, scientific evidence is lacking. We investigated fatigue severity and subtypes in FMD compared to organic neurological disease. Furthermore the role of fatigue within FMD and its impact on quality of life and self-rated health were investigated.

Data from 181 patients participating in the Self-Help on the Internet for Functional motor disorders, randomised Trial was included. Data from 217 neurological controls with neuromuscular disorders (NMD) originated from a historical cohort. Fatigue was measured using the Checklist Individual Strength (CIS). Motor symptom severity, depression and anxiety were correlated to fatigue. For multivariable regression analyses, physical functioning and pain were additionally taken into account.

Severe fatigue was respectively present in 78% and 53% of FMD and NMD patients ($p<0.001$). FMD patients scored higher than NMD patients on all fatigue subdomains ($P<0.001$). In the FMD group, fatigue subdomains were correlated to depression, anxiety and partly to motor symptom severity. Quality of life was negatively associated with fatigue (OR 0.93 (0.90-0.96), $p<0.001$) and depression (OR 0.87 (0.81-0.93), $p<0.001$), but not self-rated motor symptom severity. Self-rated health was negatively associated with fatigue (OR 0.92 (0.88-0.96), $p<0.001$) and pain (OR 0.98 (0.97-0.99), $p<0.001$).

Fatigue was found to be a prevalent problem in FMD, more so than in organic neurological disease. It significantly affected quality of life and self-rated health, while other factors like motor symptom severity did not. Fatigue should be taken into account in clinical practice and treatment trials.

INTRODUCTION

Functional motor disorders (FMD) are motor disorders that cannot be explained on the basis of known organic neurological disease, and can be significantly altered by distraction or non-physiological manoeuvres [1]. Fatigue is often reported by patients with FMD in clinical practice. However, there are only few studies reporting high levels of fatigue in functional neurological symptoms in general [2] and FMD specifically [3,4]. Fatigue is a multidimensional concept and has a complex role in neurological disorders. One way to operationalize fatigue is to study self-reported severity of subdomains of fatigue, including tiredness, concentration problems, reduced motivation, and reduced activity. In other neurological disorders, like neuromuscular disorders these subdomains have been investigated [5,6], but not in FMD.

Determinants of fatigue in FMD are unknown. In neurological disorders like Parkinson's disease [7] and muscular dystrophy [8], fatigue severity was significantly influenced by depression and motor symptom severity. In FMD fatigue could be presumed to be secondary to the functional motor symptom burden, related to comorbid anxiety or depression, or could primarily be part of the phenotype.

In organic neurological disorders fatigue is one of the major factors influencing quality of life [9,10]. This might also be the case for FMD, in which quality of life is known to be as severely impaired as in Parkinson's disease [11]. Thus, understanding how fatigue influences quality of life and self-rated health in patients with FMD, could offer a more focused target for interventions.

We aimed to study the prevalence and severity of fatigue and its subdomains in FMD compared to organic neurological disorders. To determine if fatigue in FMD could be explained by motor symptom severity, depression or anxiety, correlations between these factors and fatigue subdomains have been studied. Furthermore, we aimed to investigate the degree to which fatigue predicts quality of life and self-rated health in patients with FMD, independent of severity of the motor symptoms, physical functioning, pain, depression, and anxiety.

METHODS

Design

All FMD patients included in this study participated in the ongoing Self-Help and Education on the Internet for Functional Motor Disorders Trial (SHIFT). This trial aims to determine the effect of an online education and self-help intervention. For this study baseline data was used, which was obtained before allocation to an intervention type. Participants were referred from secondary and tertiary neurology clinics all over the Netherlands. Inclusion criteria were: age older than 18 years; a diagnosis of a functional motor disorder (including functional movement disorders and functional weakness) made by a neurologist; the functional motor symptom(s) cause(s) distress or impairment in social, occupational or other important areas of functioning, regular access to the internet and ability to read the Dutch language. All patients provided informed consent and were asked to fill out online questionnaires. The SHIFT study was performed in accordance with the the ethical and legal guidelines of the University Medical Center Groningen (Medical Ethical Committee reference number: METc 2015/141, M14.150920).

The control group consisted of patients with neuromuscular disorders (NMD), which served as an organic neurological counterpart with motor symptoms. This data had been collected previously [5]. Patients were recruited from the Neuromuscular Centre of the Institute of Neurology, Radboud University Nijmegen Medical Center outpatient clinic. Neuromuscular disorders consisted of facioscapulohumeral muscular dystrophy (FSHD), adult-onset myotonic dystrophy (MD), and hereditary motor and sensory neuropathy type I (HMSN-I).

Fatigue subdomains were compared between FMD and NMD. To determine if fatigue in FMD can be explained by motor symptom severity, depression or anxiety, correlations between these measures and fatigue subdomains were made. Furthermore, we performed multivariable regression analyses with quality of life and self-rated health as outcome measures and fatigue, severity of the motor symptoms, physical functioning, pain, depression, and anxiety as predictors, to investigate the impact of fatigue on these outcomes.

Measures

The Checklist Individual Strength (CIS) was used to measure fatigue in both groups. It assesses four different subdomains. The fatigue severity subdomain consists of 8 questions concerning tiredness and physical condition and has a score range from 8 to 56. Severe fatigue is defined as a score of 35 or higher on this subdomain. The

concentration subdomain consists of five questions on concentration (score range 5-35); the motivation subdomain has four questions asking patients about motivation and planning (score range 4-28). The physical activity subdomain consists of three questions (score range 3-21). The CIS has been validated in patients with chronic fatigue syndrome [12] and healthy control subjects [13]. The scale was previously found to have a Cronbach's alpha of 0.95, with a high test-retest reliability (Spearman rank correlation: 0.86) and moderate correlations with other fatigue scales, such as the vitality subscale of the SF36 [14].

Quality of life was measured with a single question from the WHO-QoL questionnaire: "How would you rate your quality of life on a 5-point Likert scale"[15]. Self-rated health was measured on a 7-point Likert scale, the Clinical Global Inventory (CGI), with the question "How would you rate your health in general". Based on previous studies in patients with non-epileptic attacks or FMD, the following covariates were selected: depression [16], anxiety [17], pain [18], physical functioning and motor symptom severity. Severity of all present functional motor symptoms combined was measured using a 7-point Likert scale for self-rated severity (1=no motor symptoms, 7=very severe motor symptoms). Physical function and pain were assessed using the respective subdomains of the RAND36 health-related quality of life questionnaire which is a Dutch translation of the Short-form 36 questionnaire. These subdomains range from zero to 100 with zero reflecting bad quality of life and functioning and 100 optimal functioning. The Patient Health Questionnaire 9 (PHQ-9) sum score was used to assess depressive symptoms (scores 0-27), and the generalized anxiety disorders questionnaire 7 (GAD7) for anxiety (scores 0-14).

Statistical analyses

All data was analyzed in SPSS software, version 23. Patients were excluded from all analyses when data of the Checklist Individual Strength was missing. For between group analyses, unpaired students t-test were used for normally distributed data, and Mann-Whitney U or Chi-squared tests for non-normally distributed or ordinal data. Correlations between fatigue, motor symptom severity, depression and anxiety were calculated using Spearman's rho.

For the association between fatigue and both quality of life and self-rated health, multivariable ordinal logistic regression models were used. Motor symptom severity, physical functioning, pain, depression and anxiety were included as covariates in the multivariable models. To avoid multicollinearity between subdomains and with depression and physical functioning, of all fatigue subdomains, only the subdomain

fatigue severity was included. Models were tested for multicollinearity. Data was directly entered into the multivariable models without univariable pretesting of candidate predictors, to avoid over-fitting [19]. If the multivariable ordinal logistic regression analysis would provide to many empty cells (cells with zero frequencies), which is expected when including continuous and ordinal variables, additional testing using dichotomized outcomes (Quality of life: Very poor and poor versus neutral, good and very good, Self-rated health: Very poor, poor and moderately poor versus neutral, good, very good, excellent) will be performed, to confirm reliability of the findings. Correction for multiple comparisons according to Bonferroni was performed.

RESULTS

In total, 181 FMD patients out of 186 who participated in the SHIFT study, filled out the CIS and were included in the analyses. Of these patients, 71% were female, with a mean age of 48 (SD 15) years at time of inclusion. FMD consisted of hyperkinetic symptoms (myoclonus, dystonia, tremor), paresis and gait disorder. Many patients had more than one motor symptom. Self-rated severity of the motor symptom(s) patients experienced was very mild in 5%, mild in 3%, moderate in 9%, marked in 27%, severe in 27% and 17% reported very severe symptoms.The control group consisted of 217 patients with a NMD, of whom 48% were female, with a mean age of 41 (SD 10) years. In the control group, 30% of patients had facioscapulohumeral muscular dystrophy (FSHD), 36% (adult-onset) myotonic dystrophy (MD) and 34% had hereditary motor and sensory neuropathy (HMSN). Data is displayed in table 1. Correction for multiple comparisons using Bonferroni resulted in a significance level of p=0.002.

	Functional Motor disorder (n=181)	**Neuromuscular disorder (n=217)**	**Test statistic**	**Df**	**P value**
Patient characteristics					
Mean age (SD)	48 years (15)	42 years (10)	t 4,6	396	P<0.001
Percentage females	71%	48%	x^2 21,3	1	P<0.001
Fatigue (CIS) median score (IQR)					
Severity	44 (17)	35 (18)	U 11574	-	P<0.001
Severe fatigue (Severity scores ≥35)	78%	53%	x^2 26,7	1	P<0.001
Motivation	15 (10)	11 (8)	U 14160	-	P<0.001
Concentration	21 (15)	12 (13)	U 11266	-	P<0.001
Physical activity	14 (9)	9 (8)	U 11155	-	P<0.001

Table 1. Patient characteristics and fatigue scores. For CIS-fatigue scores: higher scores mean more fatigue. SD = Standard Deviation, IQR = interquartile range.

Fatigue in FMD compared to NMD

FMD patients scored significantly higher on all fatigue subdomains compared to the NMD control group (see table 1 and fig 1). Severe fatigue (a score of 35 or more on the fatigue severity subdomain) was present in 78% of FMD patients compared to 53% of NMD patients (p<0.001). The FMD group was significantly older and had a higher percentage of females than the NMD group. However, differences between the groups persisted after linear regression with as outcome log transformed CIS scores and predictor disorder group while adjusting for age and sex (p-values remained < 0.001).

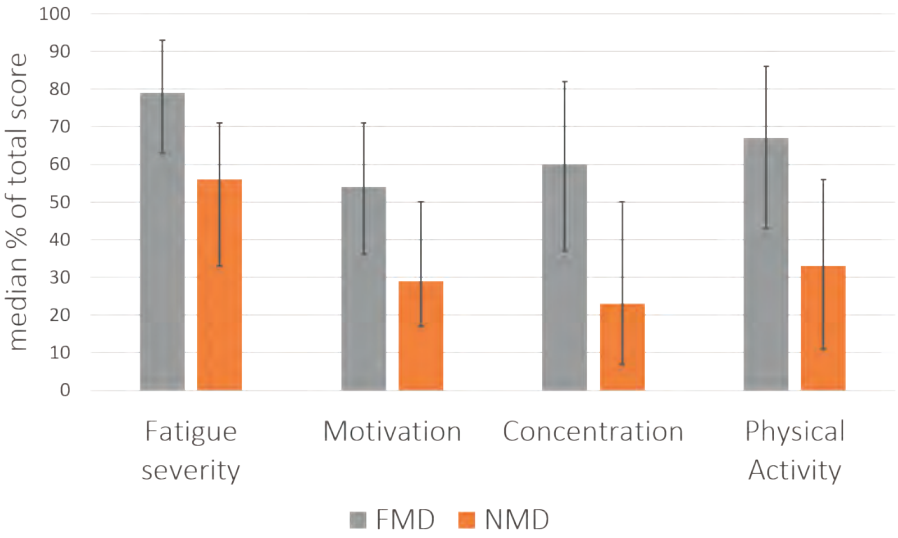


Figure 1. CIS fatigue subdomains between groups. Subdomain scores are expressed as percentage of the maximum score of the subdomain, with the minimum scores converted to zero. High scores represent a high level of fatigue. Median and interquartile range of these percentages are given for both groups.

Correlations between fatigue subdomains and depression, anxiety and motor symptom severity in FMD

To determine if depression, anxiety or motor symptom severity could be (partly) explanatory for fatigue in FMD, they were correlated to all fatigue subdomains. Correlations are displayed in table 2. Depression and anxiety were correlated with all fatigue subdomains. Severity of the functional motor symptom was correlated to fatigue severity (Spearman's rho 0.35, p<0.001) and physical activity (rho 0.29, p <0.001), but not to concentration (rho 0.19, p=0.010), and motivation (rho 0.11, p=0.125). The associations between depression and all subdomains of the CIS remained

significant when removing the one fatigue related question from the PHQ9, however, Spearman's coefficients reduced somewhat for all subdomains.

	Motor symptom severity (7-point Likert scale)		**Depression (PHQ9)**		**Anxiety (GAD7)**	
Fatigue (CIS)	Spearman's rho	P value	Spearman's rho	P value	Spearman's rho	P value
Fatigue severity	0.35	**p<0.001**	0.63	**p<0.001**	0.35	**p<0.001**
Concentration	0.11	p=0.010	0.66	**p<0.001**	0.43	**p<0.001**
Motivation	0.19	p=0.125	0.48	**p<0.001**	0.34	**p<0.001**
Physical activity	0.29	**p<0.001**	0.56	**p<0.001**	0.30	**p<0.001**

Table 2. Spearman's correlations between fatigue subdomains and motor symptom severity, depression and anxiety.

Relationship between fatigue and quality of life and self-rated health in FMD

To investigate the influence fatigue has on quality of life and self-rated health, two multivariable ordinal logistic regression analyses were performed (Table 3). Both models were tested for multicollinearity, which was ruled out.

Regarding quality of life, the analysis revealed an increase of depressive symptoms (on the PHQ9 which ranges from zero to 27) was associated with a decrease in the odds of higher quality of life, with an odds ratio of 0.87 (0.81-0.93), Wald x2 =15.57 and p<0.001. Fatigue severity, motor symptom severity, physical functioning, pain, and anxiety symptoms were not significantly associated with quality of life. To adjust for overlap between fatigue and depression (which were found to be strongly correlated, see the above), a post-hoc multivariable ordinal logistic regression was performed in which the depression score was replaced by the residuals of depression, obtained after regression with fatigue severity. The residuals of depression remained unchanged (odds ratio, 0.87 (0.81-0.93), Wald x2= 15.57 p<0.001), while fatigue severity also became a significant predictor. An increase of fatigue (on the CIS fatigue severity scale, with a score range of 8-56), was associated with an decrease of the odds of higher quality of life, with an odds ratio of 0.93 (0.90-0.96), Wald x2= 19.77, p<0.001. R-squared values for the model remained the same after this procedure.

The analysis on the outcome self-rated health revealed that fatigue severity and pain were significantly associated. An increase in fatigue was associated with a decrease in the odds of high self-rated health, with an odds ratio of 0.92 (0.88-

0.96), Wald x2= 18.70, p<0.001. An increase in pain (scored on the RAND 36, which ranges from zero to 100) was associated with a decrease in the odds of high self-rated health, with an odds ratio of 0.98 (0.97-0.99) Wald x2= 17.38, p<0.001. Motor symptom severity, physical functioning, depressive symptoms and anxiety symptoms were not significantly associated with self-rated health. The post hoc multivariable ordinal regression using the same residuals of depression, did not change this model substantially.

As both models yielded a large percentage of cells with zero frequencies, we performed additional binary logistic regression models with dichotomized quality of life and self-rated health. These models provided almost identical results.

		Quality of life (median 3, IQR 2)		**R^2=0.33**	**Self-rated Health (median 4, IQR 1)**		**R^2=0.41**
	Median (IQR)	**Odds ratio (CI)**	**Wald x2**	**p-value**	**Odds ratio (CI)**	**Wald x2**	**p-value**
Fatigue severity (CIS)	44 (17)	0.98 (0.94-1.01)	2.15	0.143	**0.92 (0.88-0.96)**	**18.70**	**<0.001**
Motor symptom(s) severity (7-point Likert scale)	6 (1)	1.0 (0.80-1.23)	0.00	0.992	1.03 (0.80-1.22)	0.10	0.758
Physical functioning (RAND 36)	40 (45)	1.01 (1.00-1.03)	3.37	0.067	1.01 (0.99-1.02)	1.06	0.304
Pain (RAND 36)	46 (57)	1.00 (0.99-1.01)	0.00	0.988	**1.02 (1.01-1.03)**	**17.38**	**<0.001**
Depression (PHQ9)	7 (9)	**0.87 (0.81-0.93)**	**15.57**	**<0.001**	0.96 (0.89-1.03)	1.37	0.242
Anxiety (GAD7)	5 (9)	0.99 (0.92-1.07)	0.03	0.869	1.02 (0.94-1.09)	0.28	0.596

Table 3. Multivariable associations between predictors and Quality of life, self-rated health in FMD (n=180). Explained variance (R^2) according to Cox and Schnell provided per model. High scores of quality of life and self-rated health represent high wellbeing/high functioning.

DISCUSSION

This study showed that 78% of FMD patients are severely fatigued, as compared to 53% of NMD patients. Fatigue subdomains motivation, concentration, and physical activity were all more severely affected in FMD compared to NMD. All fatigue subdomains were associated with depression and to a lesser degree with anxiety scores, while only the subdomains fatigue severity and physical activity

were associated with motor symptom severity. However, fatigue was significantly associated with self-rated health and with quality of life in patients with FMD, independent of motor symptom(s) severity, physical functioning, pain, depression, and anxiety.

The very high level of fatigue in FMD that was found, is remarkable. The fact that we found even higher levels of fatigue when compared to the neurological control group in this large cohort of patients underlines the scope of this problem in FMD. Our results are in line with findings from interventional studies in which fatigue was measured as a secondary outcome [4,20]. Compared to recently published norm data (n=1923), which showed 17% of healthy controls had severe fatigue when a cut-off of 35 was used [14], both FMD (78%) and NMD (53%) were more severely fatigued. However, our data do not indicate fatigue could be used diagnostically, because fatigue is high in both neurological groups and the dispersion is large in patients and healthy subjects.

We found that fatigue was clinically relevant for FMD patients, as it influences quality of life and self-rated health negatively. This is in line with findings in organic neurological disease [9,10,21]. In our data, quality of life was associated with depression and fatigue, while self-rated health was related to pain and fatigue. This might indicate patients perceive quality of life to be more strongly related to a mental state of wellbeing, while their health status would be linked to physical symptoms. The rather counterintuitive finding that motor symptom severity did not contribute to quality of life or self-rated health is not unique for FMD. The same was found in other neurological disorders, like cervical dystonia and early Parkinson's Disease [22,23].

The suggestion that fatigue in FMD could be totally explained by the burden of functional motor symptoms or an expression of affect was not supported by our data. Motor symptoms were only correlated to some of the fatigue subdomains. Depression was correlated to fatigue, however depression scores were remarkably lower than anticipated from the literature [24], while fatigue scores were much higher. That leaves us with the question if fatigue could be a core feature and part of the phenotype of FMD.

An important shared element of fatigue and FMD is that tasks require more effort than they normally would. In fatigue, it has been hypothesised that a mismatch of expectations and sensory feedback results in this altered perception of effort. Impairment of sensory attenuation would be a key element of this mechanism

[25]. Sensory attenuation is the phenomenon in healthy subjects, of a reduction of perceived intensity of sensation when a movement is self-generated (opposed to externally generated) and has interestingly also been found to be impaired in FMD [26]. Altered perception of voluntary and involuntary movements originating from a mismatch in expectations and feedback, are considered part of the explanation of the mechanism behind FMD [27], which aligns nicely with the above hypothesis to explain fatigue. Enhanced attention towards motor execution is considered another element within this framework. Abnormally enhanced attention towards execution and processing of movement and cognition, could be one of the factors causing perceived enhanced effort, both in motor symptoms and fatigue in FMD.

Although this is the largest study into fatigue in FMD including a control group, the following limitations should be taken into account. There is conceptual overlap between fatigue and depression and anxiety, which is also reflected in our measures. We have tried to minimize this by using the CIS fatigue severity subdomain for the multivariable analyses, since this subdomain does not include questions on mood or anhedonia. In addition, we have performed correlation analyses of the depression scale while excluding the fatigue question, which did not fundamentally change any of our conclusions. Also, the choice of any organic control group for FMD is debatable. NMD share characteristics like motor impairment and the association with fatigue with FMD, but do not display the same heterogeneity in symptomatology as FMD. Lastly, there are no standardised methods for measuring outcome of the severity of functional motor symptoms, which is hindered by the heterogeneous nature of FMD (the high variability in the number of symptoms, percentage of the day that symptoms occur and (number of) body parts affected). We chose for one combined self-rated Likert scale, as this was seen to reflect severity overall per patient in the most meaningful way, and provided the possibility to compare this severity between patients. The obvious downside of this approach is a loss of fine-grained information and the risk of limited variability of the data that comes with the use of a Likert scale.

In conclusion, a large number of patients with FMD experience severe fatigue, also compared to patients with organic neurological disorder. Fatigue is an important factor in FMD and is significantly associated with reduced quality of life and lower self-rated health in these patients, irrespective of the severity of the functional motor symptoms or the presence of comorbid pain or mood symptoms. The role of fatigue in FMD should therefore be recognized in clinical practice. Intervention studies in Multiple Sclerosis show improvement of fatigue after resistance training

and mindfulness [28–30]. Our results suggest FMD patients might benefit from interventions focussed on fatigue as well.

Conflict of interests: On behalf of all authors, the corresponding author states that there is no conflict of interest

Funding: J.M. Gelauff has received a grant from the Unversity Medical Center Groningen GSMS graduate school funding her PhD and a research grant from the Fund 'Fonds Psychische Gezondheid' for conducting the SHIFT study. None of the other authors report conflict of interest.

REFERENCES

1. M.J. Edwards, A. Fotopoulou, I. Pareés (2013), Neurobiology of functional (psychogenic) movement disorders. Curr. Opin. Neurol. 26:442–7. doi:10.1097/WCO.0b013e3283633953.
2. A.J. Carson, J. Stone, C.H. Hansen, R. Duncan, J. Cavanagh, K. Matthews, G. Murray, M. Sharpe (2014) Somatic symptom count scores do not identify patients with symptoms unexplained by disease: a prospective cohort study of neurology outpatients. J. Neurol. Neurosurg. Psychiatry. 86:295-301. doi:10.1136/jnnp-2014-308234.
3. G. Nielsen, L. Ricciardi, B. Demartini, R. Hunter, E. Joyce, M.J. Edwards (2015) Outcomes of a 5-day physiotherapy programme for functional (psychogenic) motor disorders. J Neurol. 262: 674–681. doi:10.1007/s00415-014-7631-1.
4. G. Nielsen, M. Buszewicz, F. Stevenson, R. Hunter, K. Holt, M. Dudziec, L. Ricciardi, J. Marsden, E. Joyce, M. Edwards (2017) Randomised feasibility study of physiotherapy for patients with functional motor symptoms, J. Neurol. Neurosurg. Psychiatry. 88:484–490. doi:10.1136/jnnp-2016-314408.
5. J.S. Kalkman, M.J. Zwarts, M.L. Schillings, B.G.M. van Engelen, G. Bleijenberg (2008) Different types of fatigue in patients with facioscapulohumeral dystrophy, myotonic dystrophy and HMSN-I. Experienced fatigue and physiological fatigue, Neurol. Sci. 29:238–240. doi:10.1007/s10072-008-0949-7.
6. J.S. Kalkman, M.L. Schillings, S.P. Van Der Werf, G.W. Padberg, M.J. Zwarts, B.G.M. Van Engelen (2005) Experienced fatigue in facioscapulohumeral dystrophy , 76:1406–1410. doi:10.1136/jnnp.2004.050005.
7. F. Stocchi, M.D. Amelio, M.F. De Pandis, G. Fabbrini, C. Pacchetti, G. Pezzoli, C. Iannacone, M. Zappia (2014) Prevalence of fatigue in Parkinson disease and its clinical correlates, Neurol. July. 83:215–220. doi:10.1212/WNL.0000000000000587.
8. K.N. Alschuler, M.P. Jensen, M.C. Goetz, A.E. Smith, A.M. Verrall, I.R. Molton (2012) Effects of pain and fatigue on physical functioning and depression in persons with muscular dystrophy, Disabil. Health J. 5:277–283. doi:10.1016/j.dhjo.2012.07.002.
9. F. Cantor (2010) Central and Peripheral Fatigue: Exemplified by Multiple Sclerosis and Myasthenia Gravis PMRJ. 2:399–405. doi:10.1016/j.pmrj.2010.04.012.
10. S. Pittion-vouyovitch, M. Debouverie, F. Guillemin, N. Vandenberghe (2006) Fatigue in multiple sclerosis is related to disability , depression and quality of life, 243:39–45. doi:10.1016/j.jns.2005.11.025.
11. K.E. Anderson, A.L. Gruber-Baldini, C.G. Vaughan, S.G. Reich, P.S. Fishman, W.J. Weiner, L.M. Shulman (2007) Impact of psychogenic movement disorders versus Parkinson's on disability, quality of life, and psychopathology, Mov. Disord. 22:2204–2209. doi:10.1002/mds.21687.
12. J.H.M.M. Vercoulen, C.M. a Swanink, J.F.M. Fennis, J.M.D. Galama, J.W.M. Van Der Meer, G. Bleijenberg (1994) Dimensional assessment of chronic fatigue syndrome, J. Psychosom. Res. 38:383–392. doi:http://dx.doi.org/10.1016/0022-3999(94)90099-X.
13. A.J.H.M. Beurskens, U. Bültmann, I. Kant, J.H.M.M. Vercoulen, G. Bleijenberg, G.M.H. Swaen (2000) Fatigue among working people: validity of a questionnaire measure, 57:353–357.
14. M. Worm-smeitink, M. Gielissen, L. Bloot, H.W.M. Van Laarhoven, B.G.M. Van Engelen (2017) The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength, J. Psychosom. Res. 98:40–46. doi:10.1016/j.jpsychores.2017.05.007.
15. T.H.E.W. Group (1998) Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment, 551–558.

16. S.G. Jones, T.J. O' Brien, S.J. Adams, R. Mocellin, C.J. Kilpatrick, R. Yerra, J.H. Lloyd, D. Velakoulis (2010) Clinical characteristics and outcome in patients with psychogenic nonepileptic seizures., Psychosom. Med.72:487–497. doi:10.1097/PSY.0b013e3181d96550.

17. I. Karakis, G.D. Montouris, C. Piperidou, M.S. Luciano, K.J. Meador, A.J. Cole (2014) Patient and caregiver quality of life in psychogenic non-epileptic seizures compared to epileptic seizures, Seizure. 23:47–54. doi:10.1016/j.seizure.2013.09.011.

18. R. Zutt, J.M. Gelauff, M. Smit, J.C. van Zijl, J. Stone, M.A.J. Tijssen (2017) The presence of depression and anxiety do not distinguish between functional jerks and cortical myoclonus, Park. Relat. Disord. 45:90–93. doi:10.1016/j.parkreldis.2017.09.023.

19. M.A. Babyak (2004) What You See May Not Be What You Get: A Brief, Nontechnical Introduction to Overfitting in Regression-Type Models. Psychosom. Med. 66:411–421. doi:10.1097/01.psy.0000127692.23278.a9.

20. M. Sharpe, J. Walker, C. Williams, J. Stone, J. Cavanagh, G. Murray, I. Butcher, R. Duncan, S. Smith, A. Carson (2011) Guided self-help for functional (psychogenic) symptoms: A randomized controlled efficacy trial. Neurology. 77:564–572. doi:10.1212/WNL.0b013e318228c0c7.

21. P. Barone, A. Antonini, C. Colosimo, R. Marconi, L. Morgante, T.P. Avarello, E. Bottacchi, A. Cannas, G. Ceravolo, R. Ceravolo, G. Cicarelli, R.M. Gaglio, R.M. Giglia, F. Iemolo, M. Manfredi, G. Meco, A. Nicoletti, M. Pederzoli, A. Petrone, A. Pisani (2009) The Priamo Study : A Multicenter Assessment of Nonmotor Symptoms and Their Impact on Quality of Life in Parkinson ' s Disease. 24:1641–1649. doi:10.1002/mds.22643.

22. B. Müller, J. Assmus, K. Herlofson, J.P. Larsen, O.B. Tysnes (2013) Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. Park. Relat. Disord. 19:1027–1032. doi:10.1016/j.parkreldis.2013.07.010.

23. M. Smit, A.S.J. Kamphuis, A.L. Bartels, V. Han, R.E. Stewart, I. Zijdewind(2016) Fatigue, Sleep Disturbances, and Their Influence on Quality of Life in Cervical Dystonia Patients, 4:517-523 doi:10.1002/mdc3.12459.

24. S. Kranick, V. Ekanayake, V. Martinez, R. Ameli, M. Hallett, V. Voon (2011) Psychopathology and psychogenic movement disorders, Mov. Disord. 26:1844–1850. doi:10.1002/mds.23830.

25. A. Kuppuswamy (2017) The fatigue conundrum. Fatigue : the unexplained phenomenon. 140:2240-2245. doi:10.1093/brain/awx153.

26. I. Pareés, H. Brown, A. Nuruki, R.A. Adams, M. Davare, K.P. Bhatia, K. Friston, M.J. Edwards (2014) Loss of sensory attenuation in patients with functional (psychogenic) movement disorders. 137:2916–2921. doi:10.1093/brain/awu237.

27. M.J. Edwards, R. A. Adams, H. Brown, I. Pareés, K.J. Friston (2012) A Bayesian account of ¨hysteria,". Brain. 135:3495–3512. doi:10.1093/brain/aws129.

28. U. Dalgas, E. Stenager, J. Jakobsen, T. Petersen, H.J. Hansen (2010) Fatigue, mood and quality of life improve in MS patients after progressive resistance training. 16:480–490. doi:10.1177/1352458509360040.

29. K.J. Dodd, N.F. Taylor, N. Shields, D. Prasad, E. Mcdonald (2011) Progressive resistance training did not improve walking but can improve muscle performance, quality of life and fatigue in adults with multiple sclerosis : a randomized controlled trial. 17:1362–1374. doi:10.1177/1352458511409084.

30. P. Grossman, L. Kappos, H. Gensicke, M. D'Souza, D.C. Mohr, I.K. Penner, C. Steiner (2010) MS quality of life, depression, and fatigue improve after mindfulness training: A randomized trial, Neurology. 75:1141–1149. doi:10.1212/WNL.0b013e3181f4d80d.

Chapter 3.

The presence of depression and anxiety do not distinguish between functional jerks and cortical myoclonus

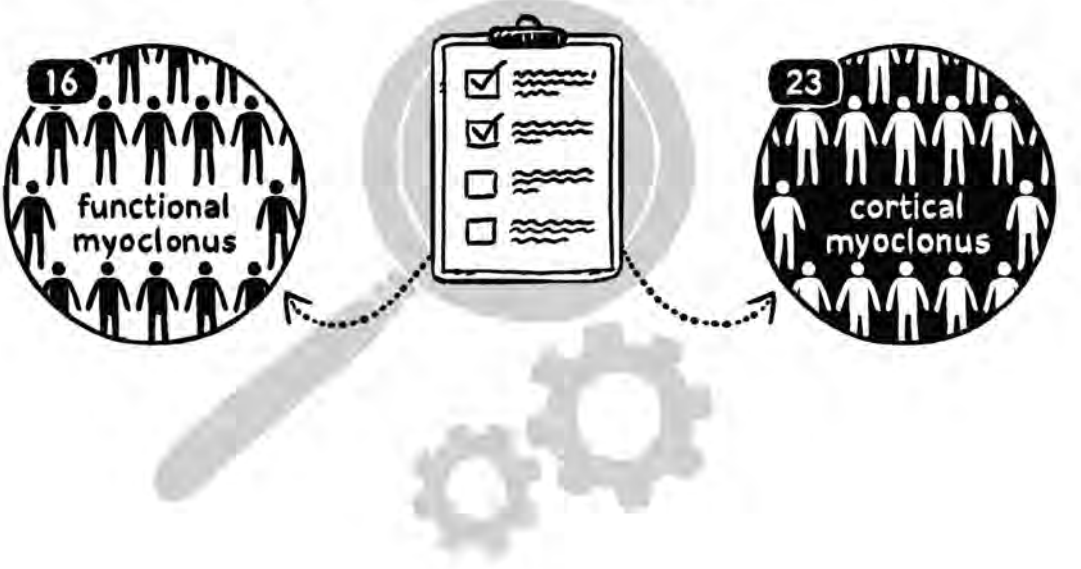
Zutt R*, Gelauff JM*, Smit M, Zijl, van JC, Stone J, Tijssen MAJ
*Both equally contributed

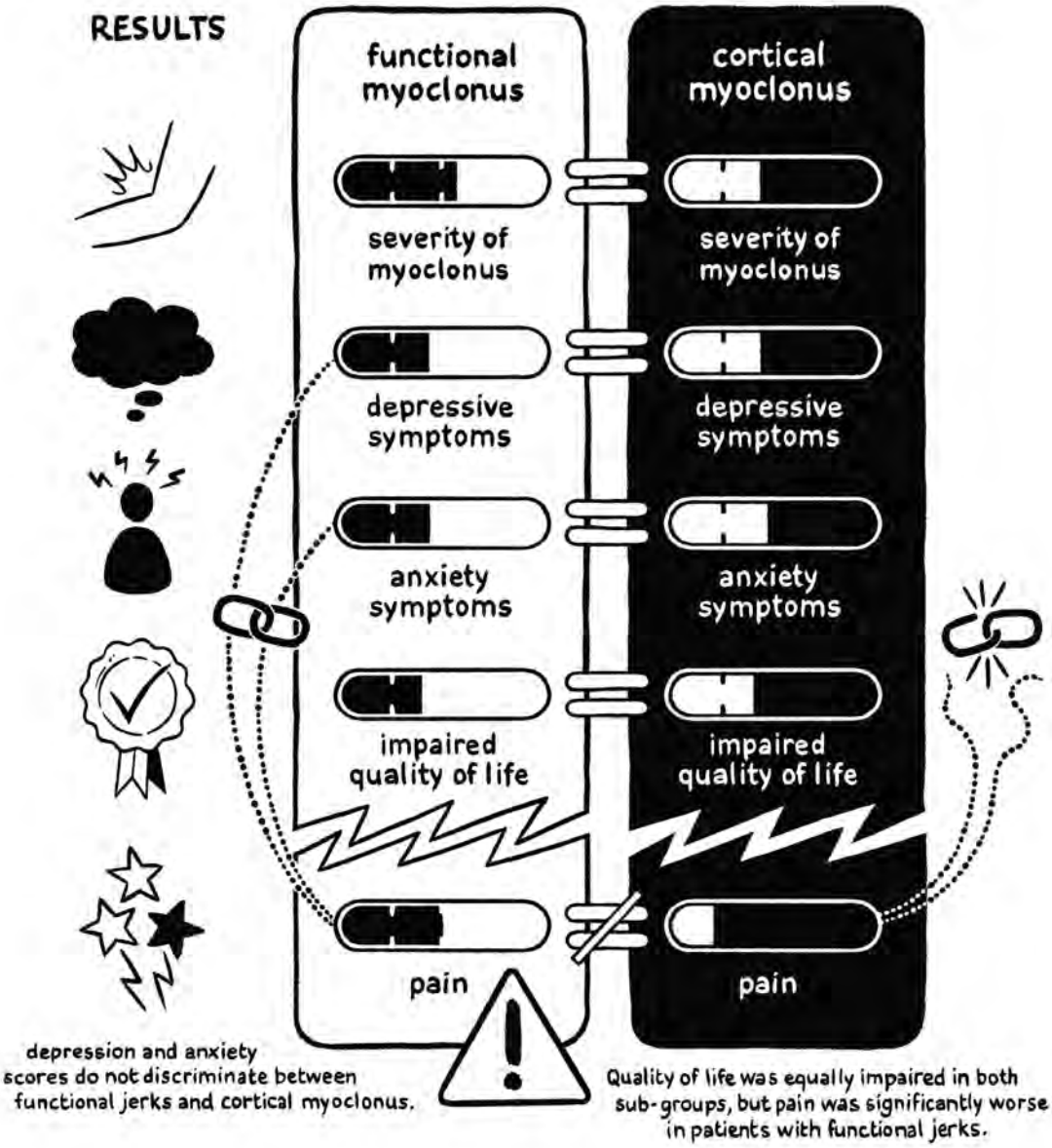
Article published in Parkinsonism and Related Disorders, 2017. Doi: 10.1016/j.parkreldis.2017.09.023

3. Are there differences in anxiety, and depressive symptoms, pain or fatigue between patients with functional and cortical myoclonus/jerky movements?

METHODS

Questionnaires, two groups:
16 patients with functional myoclonus and
23 patients with cortical ('organic') myoclonus




RESULTS
functional myoclonus
cortical myoclonus
severity of myoclonus
severity of myoclonus
depressive symptoms
depressive symptoms
anxiety symptoms
anxiety symptoms
impaired quality of life
impaired quality of life
pain
pain
depression and anxiety scores do not discriminate between functional jerks and cortical myoclonus.
Quality of life was equally impaired in both sub-groups, but pain was significantly worse in patients with functional jerks.

ABSTRACT

Functional movement disorders are accompanied by a high occurrence of psychopathology and cause serious impairments in quality of life. However, little is known about this in patients with functional jerks and no comparison has been made between patients with functional jerks and organic myoclonus. This case control study compares the occurrence of depression, anxiety and quality of life (HR-QoL) in patients with functional jerks and cortical myoclonus.

Patients with functional jerks and cortical myoclonus, consecutively recruited, were compared on self-rated anxiety (Beck Anxiety Inventory), depression (Beck Depression Inventory), health-related quality of life (RAND-36), and myoclonus severity (UMRS and CGI-S rating scales).

Sixteen patients with functional jerks and 23 with cortical myoclonus were evaluated. There was no significant difference in depression (44% vs. 43%) or anxiety (44% vs. 47%) scores between groups. The HR-QoL was similarly impaired except that functional jerks patients reported significantly more pain ($p < 0.05$). Only in the functional jerks group myoclonus severity correlated with depression and anxiety.

Depression and anxiety scores are high and do not discriminate between functional jerks and cortical myoclonus. Quality of life was equally impaired in both sub-groups, but pain was significantly worse in patients with functional jerks.

INTRODUCTION

Functional movement disorders (FMD) are disabling involuntary movements, which can be defined by incongruence with known neurological pathology and the influence manoeuvres like distraction and suggestion. One of the manifestations of FMD is functional jerks (myoclonus) (FJ), which has a prevalence amongst FMD of approximately 15% [1].

FJ is characterized by an acute onset of jerks with a slow or variable burst duration, an inconsistent distribution, and reduction with distraction [2]. Clinical discrimination between FJ and organic myoclonus can be very difficult, even for world class experts [3]. In these cases, electrophysiological testing aids in the diagnosis of FJ, especially with the finding of a pre-movement or Bereitschaftspotential with back-averaging. Accurate and early diagnosing of FJ is important as prompt treatment improves patient's outcome [4]. There is no evidence on specific therapy for FJ, but patient education and specialized physiotherapy are considered increasingly important in the treatment of FMD [5].

Symptoms of depression and anxiety are more common in FMD than in healthy controls, with 37,1%-61% lifetime depression and 20% - 21% generalised anxiety disorder in two key publications [6]. Although psychopathology has been found to be high in FMD [7], this is not unique for FMD as organic movement disorders are also often accompanied by psychopathology [8-10]. Studies comparing FMD with organic neurological disorders found either more affective disorders and anxiety in FMD, or equal prevalences [6]. Furthermore, previous studies reported a similar level of impairment of the quality of life and daily functioning, for example when comparing FMD with Parkinson's Disease [7,11]. In multiple movement disorders there is an ongoing discussion whether psychiatric co-morbidity are primary and part of the phenotype or a secondary consequence of the motor disorder [8,12].

Little is known about the psychiatric co-morbidity in patients with FJ, and, to date, there has been no systematic comparison with an appropriate control group. In our study we explored the depression and anxiety rate, and whether these psychiatric symptoms and the perceived health related quality of life could discriminate between FJ and cortical myoclonus (CM). Based on the literature, our hypothesis is that patients with FJ experience more symptoms of depression, anxiety, and have a greater impairment of their quality of life.

METHODS

Recruitment

Adult patients with FJ and CM were consecutively recruited from both the outpatient clinic and the ward of the Neurology department of our tertiary referral centre between May 2014 and June 2016. Patients were excluded if they were aged less than 16, or were judged to have significant cognitive impairment interfering with ability to complete measures. In all patients a comprehensive history was taken, including age at onset, co-existing neurological symptoms, and non-neurological co-morbidity. All subjects previously participated in a study about the value of electrophysiological testing in determination of the myoclonus subtype (article under review).

The Ethical Board of the University Medical Center Groningen (UMCG) approved the study (Number M14.157933).

Motor assessment

All patients underwent a medical history, protocolled videotaped clinical examination and electrophysiological testing. The diagnosis CM or FJ was made by a movement disorder specialist (MT) based on clinical characteristics. Co-existing neurological symptoms including additional movement disorders were recorded.

Severity of myoclonus was scored by two independent experts using the modified versions of the Unified Myoclonus Rating Scale (UMRS) [13] and the 7 point Global Clinical Impression – Severity (GCI-S) scale [14]. The average score of the two experts was used.

Psychiatric and quality of life assessment

Participants were asked to fill out a questionnaire consisting of the Beck anxiety Inventory (BAI) [15], and the Beck depression inventory (BDI) [16]. For the BDI, we used a cut-off score of 10 or higher to distinguish depressive from non-depressive patients, the range for mild depression was 10-19, moderate 19-29 and severe 30-63 [16]. For the BAI the same scores were used to divide symptoms into no, mild, moderate and severe anxiety [17]. Three items on the BAI concerning trembling or shaking of several body parts were excluded from analysis, without adjustment of the marking of the BAI, as these questions are inherent to the movement disorders studied. The RAND 36 questionnaire, a Dutch validated version of the SF36 was used for measuring quality of life [18].

Statistical analysis

Chi-square tests were used for categorical variables and Mann-Whitney U tests for ordinal and continuous not-normally distributed data in SPSS 23. When differences between groups were found, odds ratios were calculated using binominal logistic regression analysis, to provide predictive value of the factor for being in one of the groups. Inter-rater reliability for video motor scoring was assessed using the intra-class correlation coefficient (ICC) (Two way mixed, consistency, average measures). Correlations between physical functioning (RAND-36 subscale), depression (BDI), anxiety (BAI) and symptom severity (CGI), were calculated using Spearman's correlation in both groups. No violations were noted of the completed statistical analyses. All statistical tests were two-sided. The p-values of <0.05 were considered as statistically significant.

RESULTS

Participants characteristics

Forty-seven adult patients, including 27 with CM and 20 FJ were recruited. Three CM cases were excluded from the study due to cognitive problems and five cases (4FJ and 1CM) had not completed the questionnaires. In total 39 patients; 16 FJ (69% female, median age at examination 32 years) and 23 CM patients (52% female, median age at examination 30 years) participated in the study. The severity of myoclonus on the UMRS was significantly higher for FJ (FJ:16.5, CM: 5.7) without a significant difference in CGI-S (FJ:4, CM:3) with a good ICC between raters (ICC UMRS = 0.98 (95% CI: 0.95-0.99) / ICC GCI-S = 0.82 (95% CI: 0.67- 0.91)). Co-existing neurological symptoms were detected in five of the 20 FJ and in nine of the 27 CM patients (Table 1). In the CM group, in 15/23 cases an aetiological diagnosis was made; five had an acquired cause, 10 cases were thought to have a genetic origin of which a causative gene mutation was found in seven cases (see Supplementary Table 1).

The demographic features are shown in Table 1.

	CM (n=23)	FJ (n=16)
Female N (%)	12 (52%)	11 (69%)
Age at examination, median (IQR)	30 (32)	32 (38)
Age at onset of myoclonus, median (IQR)	17 (39)	25 (36)
Total UMRS, median (IQR)	**5,7 (15)**	**16,5 (14)***
Total GCI-S, median (IQR)	3 (4)	4 (4)
Medical history		
epilepsy	5	0
cognitive problems	4	0
structural brain damage	3	1
Other neurological symptoms		
dystonia	5	0
ataxia	4	0
spasticity	0	1
other functional symptoms	0	4
Median RAND-36 scores (IQR)		
Physical functioning	60 (56)	75 (63)
Social functioning	63 (38)	63 (59)
Role limitation physical	50(100)	12,5 (94)
Role limitation emotional	100 (100)	100 (50)
Mental health	76 (32)	78 (20)
Vitality	50 (30)	50 (30)
Pain	**80 (33)**	**49 (52)***
General health perception	40 (15)	50 (35)
Expected health change	50 (25)	50 (50)
Median BDI, range (cut-off scores)	9 (0 - 25)	7 (0 - 43)
No depression (0-9)	13	9
Mild depression (10-18)	7	4
Moderate depression (19-29)	3	1
Severe depression (30-63)	0	2
Median BAI Range (cut-off scores)	7 (0 - 26)	7 (3 - 28)
No anxiety (0-9)	12	9
Mild anxiety (10-18)	7	4
Moderate anxiety (19-29)	4	3
Severe anxiety (30-63)	0	0

Table 1. Demographic features, psychiatric co-morbidity and quality of life in functional jerks versus cortical myoclonus patients. CM = cortical myoclonus, FJ=functional jerky movements.

Occurrence of depression, anxiety, and health related quality of life

As is shown in Table 1, in the FJ group, 7/16 (44%) met criteria for a mild to severe depression and in the CM group this was 10/23 (43%). The median depression score on the BDI was not significantly different between the FJ and CM groups (FJ: 7 (0-

43), CM: 9 (0-25), p=0.72). Seven of 16 (44%) FJ patients and 11/23 (48%) CM patients met criteria for mild to severe anxiety. The median BAI score was not significantly different for FJ (6 (0-28)) compared to CM patients (7 (0-26)).

On all subdomains of HR-QoL FJ and CM patients were equally impaired, except for the subdomain of pain. FJ patients reported significantly more pain (FJ vs CM median 49 (IQR 52) vs median 80 (IQR 33), p < 0.05). Details about HR-QoL subdomains and severity of depression and anxiety can be found in Table 1.

As is shown in Table 2, myoclonus severity was correlated to both depression and anxiety in the FJ group, but not in the CM group. Pain was correlated to physical functioning in CM but not in FJ.

	Physical functioning (RAND36)		**Myoclonus severity (mean CGI-S)**	
	Functional jerks (FJ)	**Cortical myoclonus (CM)**	**Functional jerks (FJ)**	**Cortical myoclonus (CM)**
Myoclonus severity (mean CGI-S)	Rho -0,08 P=0.77	Rho -0,11 P=0.61	X	X
Depression (BDI)	Rho -0,27 P=0.33	Rho -0.12 P=0.60	**Rho 0.49, p = 0.05**	Rho 0.18, p = 0.42
Anxiety (BAI -corrected)	Rho -0,03 P=0,91	Rho -0.02 P=0.91	**Rho 0.73, p <0.05**	Rho 0.36, p = 0.09
Pain (RAND36)	Rho 0.40 P=0,12	**Rho 0.47 p <0.05**	Rho -0,25 P=0,34	Rho 0,31 P=0,14

Table 2: Correlations between myoclonus severity, psychiatric co-morbidity and HR-QoL. BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, CGI-S: Global Clinical Impression – Severity, CM: cortical myoclonus, FJ: functional jerks.

Statistically significant correlations using Spearman's Rho (p<0.05) are highlighted in bold.

DISCUSSION

In this prospective study, we showed functional jerks and cortical myoclonus patients had equally high depression and anxiety scores and a similar impaired health related quality of life. Patients with FJ reported significantly more pain compared to the CM group.

The occurrence of mild to severe depression and anxiety in both FJ and CM found in our cohort is high compared to the normal population. In FJ, this confirms earlier findings in several types of functional neurological disorders [7]. Psychiatric co-morbidity in a heterogeneous group of CM has not been studied before, but our results are comparable with the rates of anxiety and depression reported in CM patients diagnosed with Familial Cortical Myoclonic Tremor and Epilepsy and Juvenile Myoclonus Epilepsy [19,20]. These findings might implicate that cortical myoclonus syndromes in general are associated with psychiatric co-morbidity. In myoclonus dystonia (M-D) psychiatric comorbidity has consistently been described [10]. However, as M-D has a subcortical anatomical origin rather than cortical, a direct comparison with CM cannot be made. All in all, the similar levels of depression and anxiety in FJ and CM underline current views that these symptoms are not diagnostically relevant for FJ. The findings do, however, emphasize the importance for treatment of looking for anxiety and depression in both patient groups [5].

Health related quality of life was similarly impaired in FJ and CM patients, as was hypothesized based on the literature [7,11]. Pain was the only HRQoL subdomain significantly higher in the FJ group (median 49 (IQR 52) vs median 80 (IQR 33), $p< 0.05$). Pain has been reported to be high in other subtypes of FMD, mainly functional (fixed) dystonia [21]. The relation between FJ and pain has not been studied before. Our finding implies that pain might be a promising diagnostic tool to discriminate FJ from other jerky movements, but this requires further studies in a larger prospective cohort.

Myoclonus severity was found to correlate with anxiety and depression scores in FJ but not CM. This might suggest that in the FJ group, there is a bidirectional relationship between anxiety/depression and myoclonus. Previous studies have shown that chronic pain negatively influences mood and quality of life [22]. However, in our cohort pain did not explain the relationship between anxiety/depression and myoclonus, as pain was not correlated to myoclonus severity. The lack of a relationship between anxiety/depression and myoclonus in CM suggest that these symptoms could be part of the CM phenotype or could be caused by other factors not taken into account in this study. To be able to determine whether the psychiatric symptoms have a primary or secondary cause, larger, preferably longitudinal, studies are required.

This study has limitations. As applies to all rare disorders, we had to study a small sample from a tertiary clinic, which improves diagnostic accuracy but might impair

generalizability. Furthermore, using the BAI might have caused an overestimation of anxiety in both groups, as it largely measures the experience of physical complaints, which are partly influenced by having myoclonus. In order to minimize this overestimation, we have excluded questions directly related to jerky movements, while retaining the cut-off value.

In conclusion, this study showed high depression and anxiety scores and a comparable impairment of the quality of life in patients with FJ and CM, with significantly more pain in the FJ group. It is important for clinicians to be aware of the high appearance of depression and anxiety in myoclonic disorders as these symptoms often require treatment. Unfortunately, the presence of depression and anxiety cannot be used as a diagnostic tool for FJ, however, pain might be a significant marker of differentiation between organic myoclonus and functional jerks.

REFERENCES

1. Factor SA, Podskalny GD, Molho ES. Psychogenic movement disorders: frequency, clinical profile, and characteristics. J Neurol Neurosurg Psychiatry 1995 Oct;59(4):406-412.
2. Apartis E. Clinical neurophysiology of psychogenic movement disorders: how to diagnose psychogenic tremor and myoclonus. Neurophysiol Clin 2014 Oct;44(4):417-424.
3. Erro R, Bhatia KP, Edwards MJ, Farmer SF, Cordivari C. Clinical diagnosis of propriospinal myoclonus is unreliable: an electrophysiologic study. Mov Disord 2013 Nov;28(13):1868-1873.
4. Gelauff J, Stone J. Prognosis of functional neurologic disorders. Handb Clin Neurol 2017;139:523-541.
5. Teodoro T, Edwards MJ. Functional movement disorders. Curr Opin Neurol 2016 Aug;29(4):519-525.
6. Stone J, Warlow C, Sharpe M. The symptom of functional weakness: a controlled study of 107 patients. Brain 2010 May;133(Pt 5):1537-1551.
7. Kranick S, Ekanayake V, Martinez V, Ameli R, Hallett M, Voon V. Psychopathology and psychogenic movement disorders. Mov Disord 2011 Aug 15;26(10):1844-1850.
8. Smit M, Kuiper A, Han V, Jiawan VC, Douma G, van Harten B, et al. Psychiatric co-morbidity is highly prevalent in idiopathic cervical dystonia and significantly influences health-related quality of life: Results of a controlled study. Parkinsonism Relat Disord 2016 Sep;30:7-12.
9. Gustafsson H, Nordstrom A, Nordstrom P. Depression and subsequent risk of Parkinson disease: A nationwide cohort study. Neurology 2015 Jun 16;84(24):2422-2429.
10. Peall KJ, Smith DJ, Kurian MA, Wardle M, Waite AJ, Hedderly T, et al. SGCE mutations cause psychiatric disorders: clinical and genetic characterization. Brain 2013 Jan;136(Pt 1):294-303.
11. Anderson KE, Gruber-Baldini AL, Vaughan CG, Reich SG, Fishman PS, Weiner WJ, et al. Impact of psychogenic movement disorders versus Parkinson's on disability, quality of life, and psychopathology. Mov Disord 2007 Nov 15;22(15):2204-2209.
12 Peall KJ, Dijk JM, Saunders-Pullman R, Dreissen YE, van Loon I, Cath D, et al. Psychiatric disorders, myoclonus dystonia and SGCE: an international study. Ann Clin Transl Neurol 2015 Nov 20;3(1):4-11.
13. Frucht SJ, Leurgans SE, Hallett M, Fahn S. The Unified Myoclonus Rating Scale. Adv Neurol 2002;89:361-376.
14. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007 Jul;4(7):28-37.
15. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988 Dec;56(6):893-897.
16. Beck AT. A systematic investigation of depression. Compr Psychiatry 1988;2:163-170.
17. de Lima Osorio F, Crippa JA, Loureiro SR. Further psychometric study of the Beck Anxiety Inventory including factorial analysis and social anxiety disorder screening. Int J Psychiatry Clin Pract 2011 Nov;15(4):255-262.
18. VanderZee KI, Sanderman R, Heyink JW, de Haes H. Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med 1996;3(2):104-122.

19. Somayajula S, Vooturi S, Jayalakshmi S. Psychiatric disorders among 165 patients with juvenile myoclonic epilepsy in India and association with clinical and sociodemographic variables. Epilepsy Behav 2015 Dec;53:37-42.

20. Coppola A, Caccavale C, Santulli L, Balestrini S, Cagnetti C, Licchetta L, et al. Psychiatric comorbidities in patients from seven families with autosomal dominant cortical tremor, myoclonus, and epilepsy. Epilepsy Behav 2016 Mar;56:38-43.

21. Schrag A, Trimble M, Quinn N, Bhatia K. The syndrome of fixed dystonia: an evaluation of 103 patients. Brain 2004 Oct;127(Pt 10):2360-2372.

22. Ozturk EA, Gundogdu I, Kocer B, Comoglu S, Cakci A. Chronic pain in Parkinson's disease: Frequency, characteristics, independent factors, and relationship with health-related quality of life. J Back Musculoskelet Rehabil 2016 dec;30:101-108.

Experimental aspects
Chapter 4.

Sense of agency in functional movement disorders: a case-control experiment using a sensory incongruence paradigm

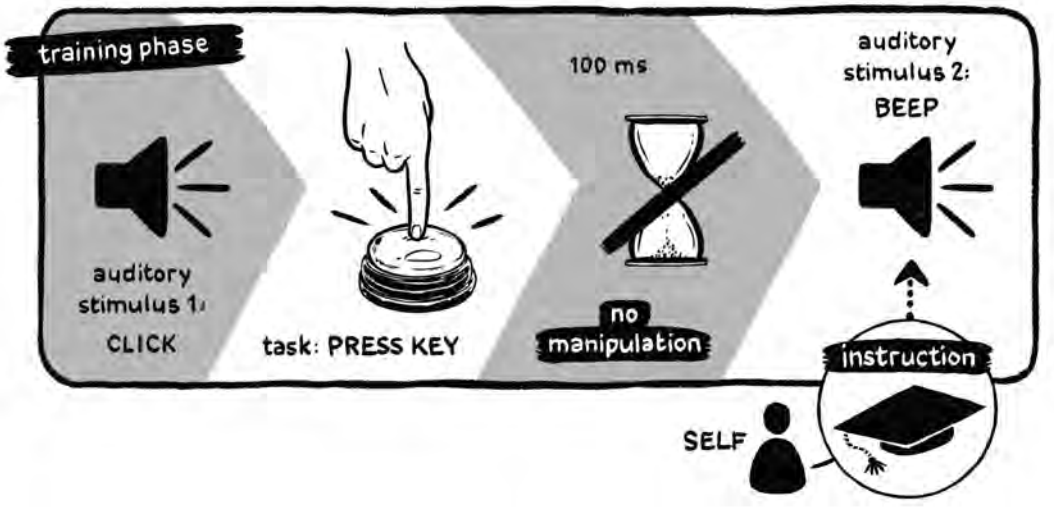
J.M.Gelauff*, J.B. Tankink*, Y.E.M.Dreissen, M.A.J.Tijssen
*authors contributed equally

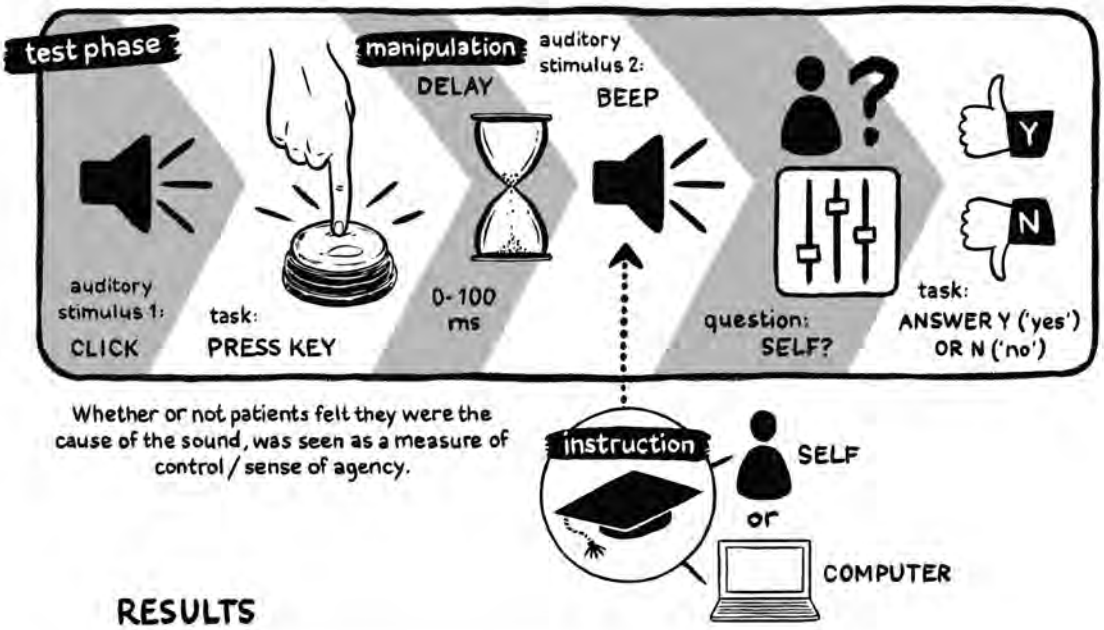
4. Is self-reported sense of agency in a motor experiment reduced in patients with functional motor disorders?

METHODS

Experiment. 2 groups: **19** functional motor disorders, **19** healthy volunteers.

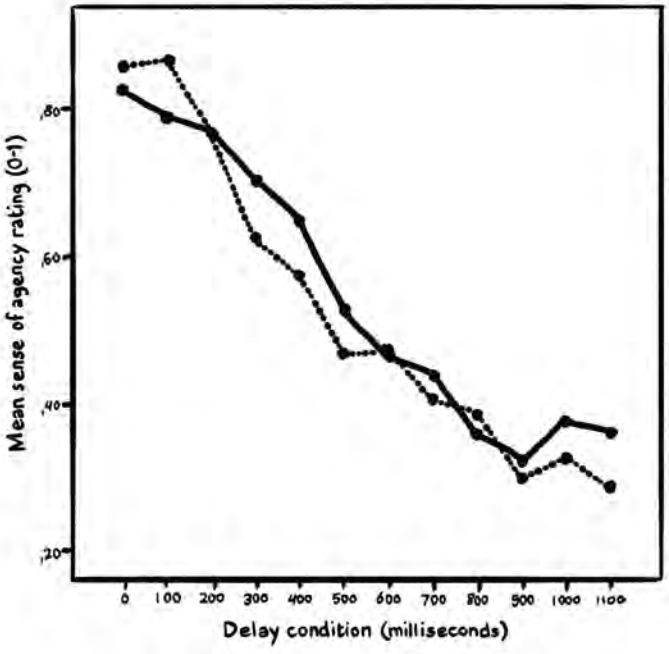
Subjects were asked to press a button after a auditory stimulus. This resulted in a response sound. In the experiment, the time between button press and response sound was manipulated with a varying delay. Patients were asked each time whether or not they were the cause of this response sound.





Whether or not patients felt they were the cause of the sound, was seen as a measure of control / sense of agency.

RESULTS



no difference between groups

Explicit Self-reported Sense of agency using an action-reaction paradigm, modulated by a time delay, was normal in patients with FMD.

ABSTRACT

We investigated whether self-reported sense of agency is reduced in patients with functional movement disorders (FMD) compared to healthy controls.

Nineteen FMD patients and nineteen healthy volunteers matched on age, gender and educational level participated. A computer-designed task based on the principle of creating sensory incongruence was used to modulate sense of agency. In this experiment subjects were asked if their action (pressing a button) caused a reaction (auditory tone) which would follow at a variable time delay (0-1100 ms).

We demonstrated impaired self-reported sense of agency in both patients and volunteers (p = .002) with increasing sensory incongruence during the experiment. No differences however were detected between groups (p = .655).

Self-reported Sense of agency using an action-reaction paradigm, modulated by a time delay creating sensory incongruence, was normal in patients with FMD.

We discuss how choices in the experimental design, may explain a lack of difference between cases and controls. Moreover, our findings offer a view on the complex and apparent multileveled nature of sense of agency. We conclude that the link between Sense of agency and its experimental markers as well as its role in FMD need to be further researched.

INTRODUCTION

It has been hypothesized that abnormal experience of (motor) action, or a reduced sense of agency, is a potential hallmark of FMD (Edwards et al., 2013). Disturbances in sense of agency– i.e. the sense of oneself as the agent of one's own (motor) actions – could explain why FMD patients report lack of control for movements that physiologically appear as voluntary (Hallet, 2010; vd Salm et al., 2012; Parees et al., 2014).

Sense of agency allows for distinction between 'self' and 'other', thereby representing an essential component of human volition and movement (Gallagher, 2000; David et al., 2008). Several theoretical models (reviewed by David et al., 2008) have been developed on sense of agency, among which the 'comparator model' is one of the most influential. It describes how Sense of agency arises from the comparison of sensorimotor plans ("efference copies") and predictions prior to movement, to post-motor sensory feedback. In case of a match between predicted movement and sensory feedback after the movement, sense of agency is present; in case of a mismatch, agency will be attributed to an external source or the motor action will be interpreted as 'failed' or 'not one's own' (Blakemore et al., 2002; Synofzik et al., 2008). Studies in FMD patients have shown altered activity in the temporo-parietal junction, which has been posed to be the neuro-anatomical substrate of these comparative processes, i.e. sense of agency (e.g. Farrer and Frith, 2002, Voon et al., 2010).

Few studies in FMD assessed sense of agency in an experimental fashion thus far. Kranick et al. (2009) found reduced intentional (action-effect) binding in FMD. This is the effect by which healthy people report the timing of a motor action and its sensory effect; they occur nearer in time when these events are considered cause-and-effect (Haggard, 2002). Since this perceptual distortion is only observed for voluntary movement - i.e. movement for which one experiences agency, intentional binding is thought to represent a marker of Sense of agency (reviewed by Moore & Obhi, 2012). Similarly, sensory attenuation, the phenomenon in which the intention of sensory sensations is reduced when a movement is self-generated, is considered as another indicator of sense of agency. Parees et al. (2014) and Macerollo et al. (2015) demonstrated loss of sensory attenuation in FMD patients and linked this to impaired Sense of agency.

In the current study, we hypothesized to reveal reduced sense of agency in patients with FMD through the principle incongruence between motor action and sensory feedback. This can be experimentally assessed by creating temporal delay between a motor action and its sensory outcome (David et al., 2008). We conducted a computer

task similar to an experiment carried out by Sato & Yasuda (2005), who demonstrated that temporal delay reduced sense of agency in healthy people. Sensory incongruence was found to alter Sense of agency in several groups of patients as well, for example in schizophrenia (e.g. Maeda et al., 2012).

METHODS

Participants

FMD patients were included from the Neurology department of the University Medical Center Groningen and the Academic Medical Center (the Netherlands). All patients with a FMD (e.g. tremor, myoclonus, dystonia), who had a minimal symptom duration of one year or more, who were aged 18 years or older and had the ability to give informed consent were invited to participate. The diagnosis was made by a movement disorders specialist, conform the current standards based on positive signs in the disease history and neurologic examination. Healthy volunteers, recruited by advertisement in the hospital and university, were matched based on age, gender and educational level; the latter was determined using the Dutch scoring system of Verhage (1964). Volunteers with (a history of) neurological symptoms of any nature were excluded from participation. Written informed consent was obtained from all participants. This study was approved by the Medical Ethical committee of the University of Amsterdam, as part of a larger study to the effect of Botulinum Toxin injections for functional movement disorders.

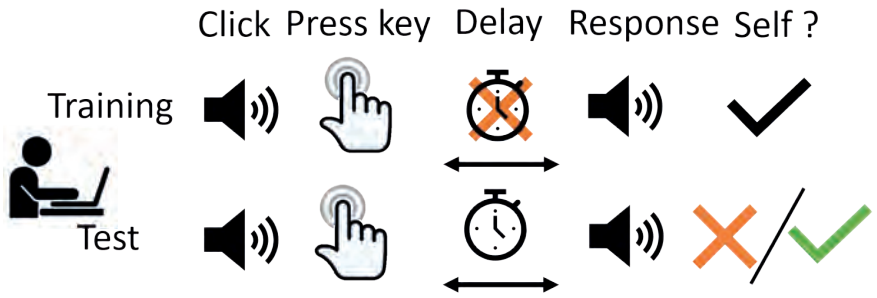
Agency Experiment

We adapted a paradigm from Sato & Yasuda (2005). In this experiment incongruence between motor action and sensory feedback is used as a model to measure (reduced) sense of agency. The incongruence that was introduced, was a temporal delay between button press and a tone response. Below a detailed description of the experiment is provided in flowchart 1. In short, patients were asked to rate whether or not they felt to have been the cause of a response sound after a self-timed button press. The crucial part of the experiment was a variable delay between these two (button press and response sound), which was unknown to the patient. Before the experiment started, there was a training phase, in which patients learned what the normal action-response time was.

Analysis

For statistical analysis, we used IBM SPSS Statistics version 22.0.0. The number of times a participant answered 'yes' (judging the tone as self-produced) resulted in

a mean reported sense of agency. For every participant, we calculated cumulative scores on the twelve different delay conditions (0 – 1100 milliseconds) throughout each of the six subsets; i.e. in case a participant responded by 'yes' three out of six times on the delay condition "500 milliseconds", mean reported sense of agency of the participant on this condition would be 0.5 (50%). Missing values were imputed using mean scores of the entire group (patients and controls) on the particular variable. A two-way repeated measures analysis of variance (ANOVA), with within-groups factor "temporal delay" and between-subject factor "group" (patient/control) was used to determine the effect of temporal delay on reported sense of agency along with potential differences between patients and controls in the extent of this effect. Statistical significance of $p < .05$ was assumed significant.



Flowchart 1: events and instructions of the agency experiment

RESULTS

Participants

19 patients with FMD and 19 healthy volunteers participated. The phenomenology of motor symptoms in the FMD patient group included myoclonus (n=8, 42%), tremor (n=6, 32%), dystonia (n=4, 21%) and gait disorder (n=2, 11%). Matching succeeded well, based on age (45.8 ± 15.6 and 45.3 ± 16.0 for patients and volunteers respectively), gender (8 males and 11 females in both groups) and educational level (5.7 ± 1.1. and 6.2 ± 0.9 respectively).

Agency Experiment Results

Analysis of results revealed that overall, temporal delay significantly lowered reported sense of agency, $F(11, 26) = 4.021$, $p = .002$. However, this effect did not differ significantly between FMD patients and healthy volunteers, $F(11, 26) = 0.782$, $p = .655$. Neither did any of the delay durations separately reveal significant differences between patients and controls. Results are presented in figure 1.

A learning effect was observed through repeated measures ANOVA with the cumulative scores of patients and controls on each of the six subsets (each consisting of the twelve different delay conditions),F (5, 32) = 4.215, p = .005, see figure 2.

Although patients had a lower mean sense of agency rating than controls on all but the first of the subsets (1-6) of conditions (0-1100 ms), a MANOVA test revealed that this was not significant on any of the subsets F (1, 36) ⩽ 0.045, p ⩾.142.

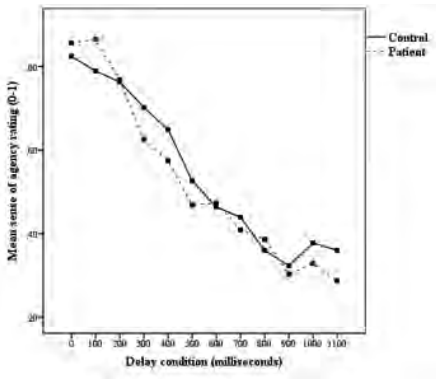


Fig. 1. Mean sense of agency rating in each delay condition.

Results of the mean reported Sense of agency by patients versus volunteers per delay condition (0-1100 ms). Reported Sense of agency is based on the number of in total 144 trials (divided into six subsets) in which a patient responded by 'yes' (judging the tone as self-produced), per delay duration, as displayed on the x-axis (no delay to 1100 milliseconds delay).

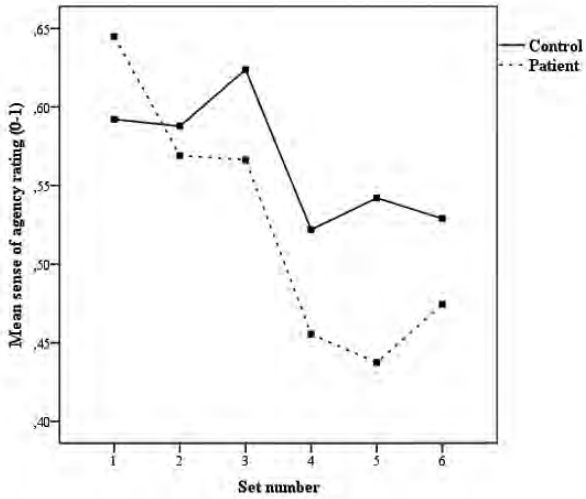


Fig. 2. Mean sense of agency rating over time.

Results of the evolution of responses in time are displayed in patients and controls, with on the x-axis the trial subset from 1 to 6. Sense of agency ratings are expressed on a scale of 0 (agency attribution to computer) to 1 (agency attribution to self), based on the number of times a patient reported the stimulus to be self-generated.

DISCUSSION

We demonstrated that creating a time delay between motor action, i.e. a voluntary movement, and a sensory outcome, i.e. an auditory tone, causing sensory incongruence, lowers self-reported sense of agency in patients with FMD as well as healthy subjects, thereby replicating previous work (e.g. Farrer and Frith, 2002; Sato and Yasuda, 2005; Maeda et al., 2012; Delorme et al., 2016). Impaired Sense of agency is thought to to play a key role in the pathophysiology of FMD (Kranick et al., 2013; Edwards et al., 2011; Edwards et al., 2013; Voon et al., 2010). Opposed to what we hypothesized, sense of agency assessed in this experiment was not lower in FMD compared to healthy controls.

Our negative findings might reflect that sense of agency is not merely a product of sensory congruence in a comparative process; instead, sense of agency might be more adequately described as a multileveled phenomenon, composed of low-level (sensorimotor), as well as high-level (cognitive), 'reflective' experiences of agency (David et al., 2008; Synofzik et al., 2007). Furthermore, the optimal-cue-integration theory sense of agency states that multiple internal and external cues, together with prior beliefs and expectations, are weighted based on their different reliabilities, eventually leading to a sense of agency (reviewed by Moore & Fletcher, 2012*)*. Perhaps, the specific cue of sensory congruence in the formation of sense of agency is unaffected in FMD, whereas cue-integration is still disturbed leading to reduced sense of agency. Moreover, the fact that previous authors found reduced sense of agency in FMD when measured through indirect markers (such as action-effect binding and sensory attenuation), whereas we did not through explicit self-report, supports the notion of different processes involved in indirect and explicit sense of agency, which has been described elsewhere (Moore & Obhi, 2012).

Finally, sense of agency is most clearly affected in FMD in relation to the motor symptoms themselves, which are perceived involuntary. Although previous studies have found altered sense of agency in FMD in tasks comprising general motor control (not related to the symptoms), our negative findings might be explained by the fact

that motor symptoms are associated with reduced sense of agency, but voluntary motor might not be.

Besides uncertainty regarding the use of explicitly reported sense of agency, there are several limitations in our study that may have contributed to the lack of differences. In general, the small sample size and heterogeneity of FMD phenotypes make this study explorative in nature and hamper bold conclusions. Furthermore, including temporal delay conditions up to 1100 milliseconds may have caused blurring of an effect around the threshold of 150-300 milliseconds, when healthy people can normally recognize temporal delay and estimations of agency may be most uncertain (Blakemore and Frith, 2003). However, the group comparison per delay duration did not reveal differences around this threshold either. Finally, every experiment is an approximation of reality. Perhaps our experiment merely shows the capacity of subjects to recognize delay, which might not translate into a sense of agency. There were no significant differences between patients and controls reaction times.

In conclusion, our results suggest that explicitly reported sense of agency, in an experiment using sensory incongruence, is not affected in FMD. This idea fits into a theoretical framework emphasizing the multileveled nature of sense of agency. It seems likely that different experimental designs refer to different levels of sense of agency. However, we believe our study offers reflections on the complexity of (studying) sense of agency as well as the unanswered questions regarding FMD pathophysiology, and warrants further research.

REFERENCES

Blakemore, S. J., Wolpert, D. M., & Frith, C. D. (2002). Abnormalities in the awareness of action. *Trends in cognitive sciences*, *6*(6), 237-242.

Blakemore, S. J., & Frith, C. (2003). Self-awareness and action. *Current opinion in neurobiology*, *13*(2), 219-224.

David, N., Newen, A., & Vogeley, K. (2008). The "sense of agency" and its underlying cognitive and neural mechanisms. *Consciousness and cognition*, *17*(2), 523-534.

Delorme, C., Roze, E., Grabli, D., Mayer, J. M., Degos, B., Vidailhet, M., & Worbe, Y. (2016). Explicit Agency in Patients with Cervical Dystonia: Altered Recognition of Temporal Discrepancies between Motor Actions and Their Feedback. *PloS one*, *11*(8), e0162191.

Edwards MJ, Moretto G, Schwingenschuh P, et al. Abnormal sense of intention preceding voluntary movement in patients with psychogenic tremor. *Neuropsychologia* 2011; 49:2791–2793

Edwards, M. J., Fotopoulou, A., & Parees, I. (2013). Neurobiology of functional (psychogenic) movement disorders. *Current opinion in neurology*, *26*(4), 442.

Farrer, C., & Frith, C. D. (2002). Experiencing oneself vs another person as being the cause of an action: the neural correlates of the experience of agency. *Neuroimage*, *15*(3), 596-603.

Hallett M. Physiology of psychogenic movement disorders. *J Clin Neurosci*. 2010;17:959–965.

Maeda, T., Kato, M., Muramatsu, T., Iwashita, S., Mimura, M., & Kashima, H. (2012). Aberrant sense of agency in patients with schizophrenia: forward and backward over-attribution of temporal causality during intentional action. *Psychiatry research*, *198*(1), 1-6.

Macerollo, A., Chen, J. C., Pareés, I., Kassavetis, P., Kilner, J. M., & Edwards, M. J. (2015). Sensory attenuation assessed by sensory evoked potentials in functional movement disorders. *PloS one*, *10*(6), e0129507.

Moore, J. W., & Fletcher, P. C. (2012). Sense of agency in health and disease: a review of cue integration approaches. *Consciousness and cognition*, *21*(1), 59-68.

Moore, J. W., & Obhi, S. S. (2012). Intentional binding and the sense of agency: a review. *Consciousness and cognition*, *21*(1), 546-561.

Pareés, I., Brown, H., Nuruki, A., Adams, R. A., Davare, M., Bhatia, K. P., ... & Edwards, M. J. (2014). Loss of sensory attenuation in patients with functional (psychogenic) movement disorders. *Brain*, *137*(11), 2916-2921.

Salm van der S.M.A., Tijssen M.A.J., Koelman J.H.T.M., Rootselaar A.F. (2012), The Bereitschaftspotential in Jerky Movement Disorders, *J Neurol Neurosurg Psychiatry* 83 (12), 1162-7

Sato, A., & Yasuda, A. (2005). Illusion of sense of self-agency: discrepancy between the predicted and actual sensory consequences of actions modulates the sense of self-agency, but not the sense of self-ownership. *Cognition*, *94*(3), 241-255.

Synofzik, M., Vosgerau, G., & Newen, A. (2008). Beyond the comparator model: a multifactorial two-step account of agency. *Consciousness and cognition*, *17*(1), 219-239.

Verhage, F. (1964). Intelligentie en leeftijd: onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar [Intelligence and age: Study with Dutch people fron age 12 to 77]. Assen: Van Gorcum.

Voon, V., Gallea, C., Hattori, N., Bruno, M., Ekanayake, V., & Hallett, M. (2010). The involuntary nature of conversion disorder. *Neurology*, *74*(3), 223-228.

Chapter 5.

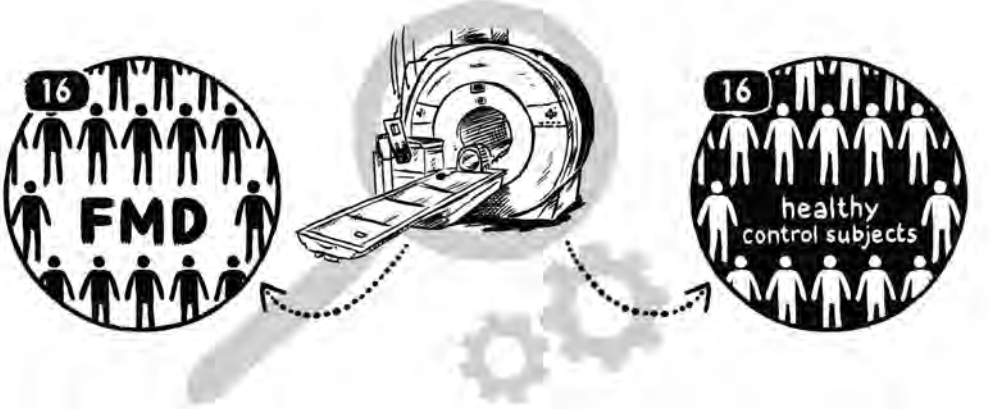
Sense of Agency and Body Scheme Representation in Functional Movement Disorders: an fMRI Study

Gelauff JM, Beudel J, Marsman JBC, Dreissen YEM, Tijssen MAJ, Jong, de BM

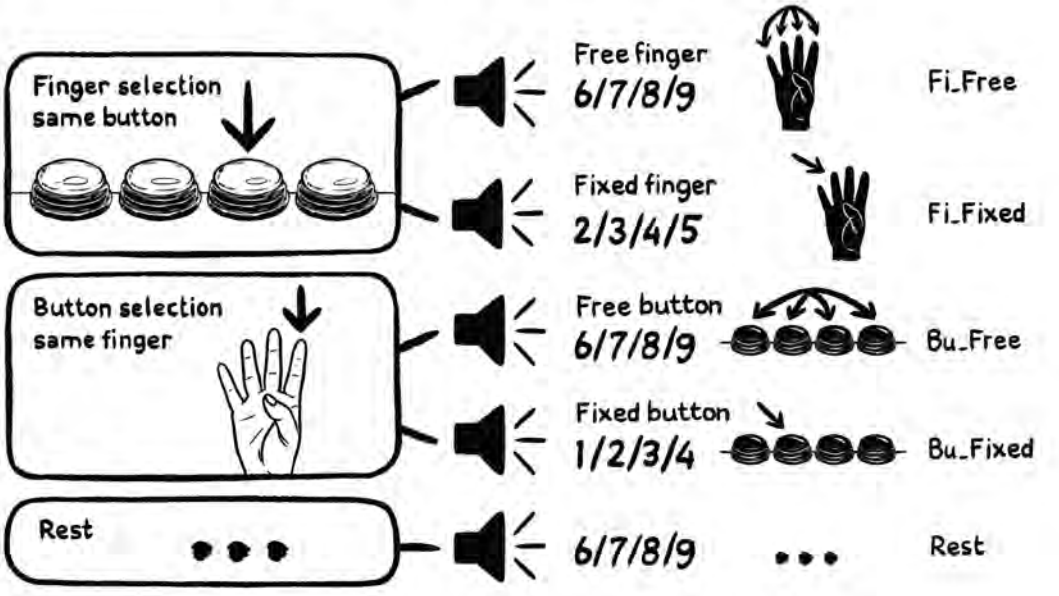
5. Are sense of agency and body scheme representation in functional motor disorders altered in a action-selection fMRI study?

METHODS

16 patients with FMD and **16** healthy control subjects performed a task during a functional MRI scan



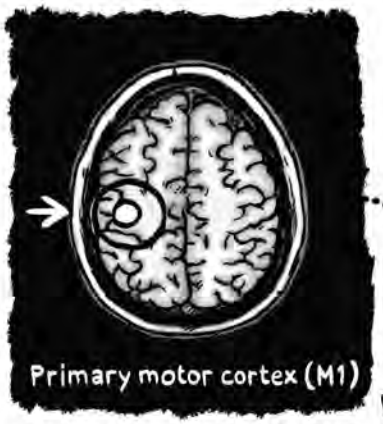
Patients had to press certain buttons using certain fingers, either with fixed instructions or with free choice.



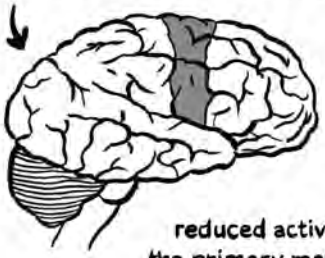
RESULTS

1.

Findings of this same experiment in only healthy subjects confirmed



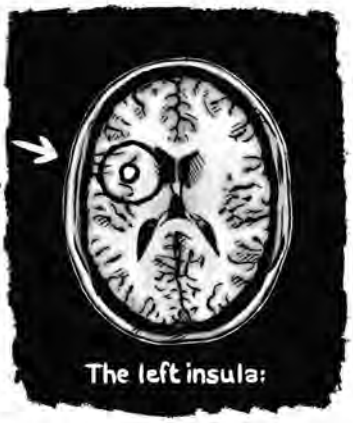
Reduced activation in FMD (all motor tasks combined)



reduced activation of the primary motor cortex corroborates impaired explicit motor control in FMD.

2.

reduced activation

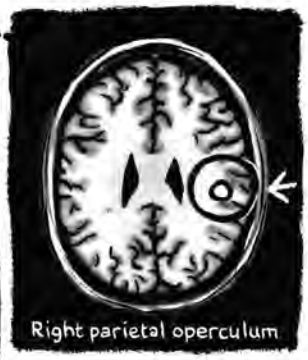


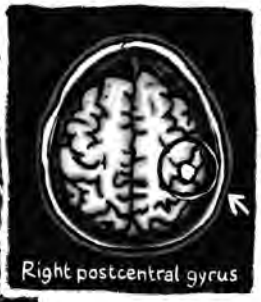
FMD reduced activation in contrast FINGER FREE → BUTTON FREE and FINGER FREE → FINGER FIXED.

Correlation between these activations and severity of the motor symptoms.

We confirmed associations of the insula with reduced sense of agency and altered perception of body scheme in FMD.

Reduced activation in patients (patients < controles) in several parietal areas





Reduced sense of agency was further underlined by our findings of reduced activations of premotor and parietal cortices, most apparent in fixed (externally cued) compared to free action selection.

ABSTRACT

In functional motor disorders, altered perception of the body and sense of agency are key aspects of the underlying mechanism.

To identify FMD-related changes in cerebral activation with fMRI in regions implicated in self-perception and sense of agency, self-referenced versus goal directed and both free and fixed action selection are assessed in patients with FMD, compared to healthy controls.

16 FMD patients and 16 matched healthy controls (HC) underwent fMRI-scanning during a motor task with alternating blocks selecting fingers (self-referenced) versus buttons (goal-directed) and free (internal) versus fixed (external) cues. Differences were analyzed using statistic parametric mapping (SPM). Regions of interest were correlated with symptom severity (spearman's rho) and studied for connectivity using psycho-physiological interactions.

We confirmed findings in HC of predominantly prefrontal and parietal activations in free versus fixed conditions, the opposite contrast showed the extrastriate visual cortex and activation along the dorsal intraparietal sulcus. In finger versus button selection, activations of the occipital and anterior parietal cortices, including the postcentral sulcus were found. In FMD compared to HC we found reduced activation of the left primary motor cortex in the conjunction of all motor conditions ($p<0.05$ FWE-corrected). The left insula of patients showed reduced activation during free finger selection compared with both fixed finger and with free button selections ($p<0.001$ uncorr), which correlated to symptom severity (Rho 0.463 ($p=0.035$)). In fixed versus free selection reduced activation of the left premotor and right parietal operculum and along the left intraparietal sulcus were key findings in patients compared to controls. Finger versus button selection showed additionally reduced activation of the right anterior cingulate and the postcentral gyrus ($p<0.001$, uncorr). Increased connectivity between the primary motor cortex and occipitotemporal cortex and reduced connectivity between the left insula and left postcentral gyrus, and between the parietal operculum and hippocampus in FMD was found ($p<0.05$ FWE-corrected).

We further specified previously reported associations of the insula with reduced sense of agency and altered perception of body scheme in FMD. Reduced sense of agency was further underlined by our findings of reduced activations of premotor

and parietal cortices, most apparent in fixed (externally cued) compared to free action selection. Finally, reduced activation of the primary motor cortex corroborates impaired explicit motor control in FMD.

INTRODUCTION

The pathophysiology of functional movement disorders (FMD) is gaining more and more interest and increasingly influences treatment strategies. The leading explanation of FMD is a Bayesian model in which biopsychosocial factors that exist in varying combinations in each patient form expectations and beliefs (I), that interact with alterations of agency (II) and attention to the self (III) [1].

Sense of agency is the perception that you are the cause of an action [2]. Consequently, a distorted sense of agency in FMD could explain the discrepancy between patients' experience that their symptoms are involuntary, while measurements of these movements indicate normal preparation of movement. For example by the presence of a Bereitschaftspotential in functional myoclonus [3]. Findings of a reduced intentional-binding effect [4] and less sensory attenuation [5], both seen as measures of sense of agency, fit with that notion.

Functional brain imaging has enabled identification of neural substrates of sense of agency such as the parietal cortex (specifically anterolateral and lateral temporo-parietal areas), the frontal and prefrontal cortex, the insula and postero-midline structures like the precuneus and posterior cingulate cortex [6, 7]. In FMD, Nahab et al. [8] explicitly studied sense of agency recently, and found that loss of movement control was associated with less response of the right anterior insula and right temporoparietal junction (TPJ) in a virtual reality paradigm.

Perception of the body and of bodily sensations, the second pillar of the mechanism of FMD is strongly linked to perception of agency. In this respect, patients have been described to over-attend their symptoms [9], while altered perception of body ownership has been demonstrated in motor FMD [10]. Also, patients with functional dystonia may experience an abnormal position of their affected body part [11].

Using functional imaging, Maurer et al made the link between sense of agency and attention to the self in FMD [12]. Using TPJ as a prespecified seed in resting state MRI, decreased functional connectivity was found between the right TPJ and the right sensorimotor cortex, cerebellar vermis, bilateral supplementary motor area (SMA), and right insula in FMD compared to healthy controls. The authors interpreted this as a combination of disturbed feed-forward motor control and distorted sensory perception, resulting in reduced sense of agency. Furthermore, a meta-analysis on

imaging in FMD showed that the insula, dorsolateral prefrontal and frontal brain areas were most consistently affected in FMD [13].

Given the stronger association of free choice responses with sense of agency, compared to fixed instructions [14], the study of Voon et al [15] is of particular interest, because their fMRI study provided further insight in such link by demonstrating reduced functional connectivity of the left SMA with bilateral dorsolateral prefrontal cortices in FMD in free versus fixed button selection. However, the effect of representation of body scheme in FMD was not studied. An extended fMRI paradigm from our group performed in healthy subjects did address both (i) representation of body scheme, by comparing self-referenced (finger) versus goal-directed (button) selection, and (ii) free versus fixed action selection [16]. This study showed prominent prefrontal activations in free versus fixed selection, with differential contributions of the dorsal prefrontal and anterior cingulate cortex in self-referenced compared to goal-directed selection. In both free selection conditions the inferior parietal cortex was bilaterally activated. This added support to novel concepts that free choice is not only associated with prefrontal regions, but also involves the parietal cortex [17–19].

In the present study we employed the Beudel paradigm [16] to investigate both self-referenced versus goal directed movement and free (internally) selected versus fixed (externally) instructed tasks in patients with FMD, compared to healthy controls. We hypothesized to find particularly FMD-related decreases in activation in prefrontal and parietal brain regions when making self-generated (free) compared to externally cued (fixed) selections. Furthermore, we expected reductions in (pre)frontal, parietal and insula activations during self-referenced (finger) movement compared to goal directed movement towards a button.

METHODS

Study design

Participants were included from the movement disorder clinics of the University Medical Center Groningen (UMCG) and the Amsterdam University Medical Center (AUMC). For this study, all participants were seen twice at the UMCG. During the first meeting, participants received instructions, were interviewed and performed a computer version of the fMRI paradigm outside the scanner. Patients were asked for the severity of the functional tremor/myclonus on a 7-point Likert scale and psychiatric co-morbidity using the BDI (Beck Depression Inventory) and BAI (Beck

Anxiety Inventory). The actual fMRI paradigm was performed approximately one week later.

Participants

Sixteen out of 17 scanned patients with a functional myoclonus or functional tremor (mean age 43 (SD 14) 50% male (n=8)) and 16 matched healthy control subjects (mean age 42 (SD 14),) were included. One patient was excluded due to hearing problems. The diagnosis of a functional myoclonus or tremor was made by an expert neurologist in movement disorders, based on clinical findings and clinical neurophysiological measurements to support the diagnosis. Only right-handed patients older than 17 were included. All subjects provided written informed consent. Exclusion criteria were incompatibility with MRI-scanning and not being able to perform the task. Educational level was university of applied sciences (Dutch: HBO) or higher in 50% of patients and 75% of controls. None of the healthy controls suffered from anxiety or depression, in the patient group depression scores on the Beck depression inventory were 8.4 on average (SD 7.9), corresponding to absent depression, while anxiety on the Beck anxiety inventory was 17.5 on average (SD 13.2), corresponding to mild anxiety (BDI and BAI range 0 – 63). In the patient group, symptom severity on the clinical global impression (CGI), rated by consensus of the investigator and the patient, was median 4 (IQR 2).

Task Paradigm

We used the paradigm previously published by Beudel et al. [16]. In this auditory instructed block-design, there were four different motor conditions and one rest condition. These were alternated, in order to test both internally and externally generated cues of which finger to use and which button to press. Figure 1 illustrates the paradigm. It worked as follows: there were four buttons and patients were instructed to use fingers 2,3,4,5. They received auditory instructions before each block indicating which condition followed, and during each condition. In the first two conditions, subjects had to use the same button (Bu), while the choice of which finger to use was either chosen by the patient (Fi_Free) or externally imposed (Fi_Fixed). In the third and fourth condition, the same finger was used (digit 2) and the choice of which button to use was either chosen by the patient (Bu_Free) or externally imposed (Bu-Fixed). The fifth condition (Rest), served as a control condition. Apart from the auditory instructions before each block, patients received auditory cues before each button press. In the free conditions (1 and 3) and the rest condition (5), these were meaningless numbers 6,7,8 and 9. In the fixed conditions, these numbers represented which finger to use, 2,3,4 or 5 (condition 2), or which button to press

1,2,3 or 4 (condition 4). See figure 1 for graphical depiction of the task conditions. Response choices and reaction times were logged.

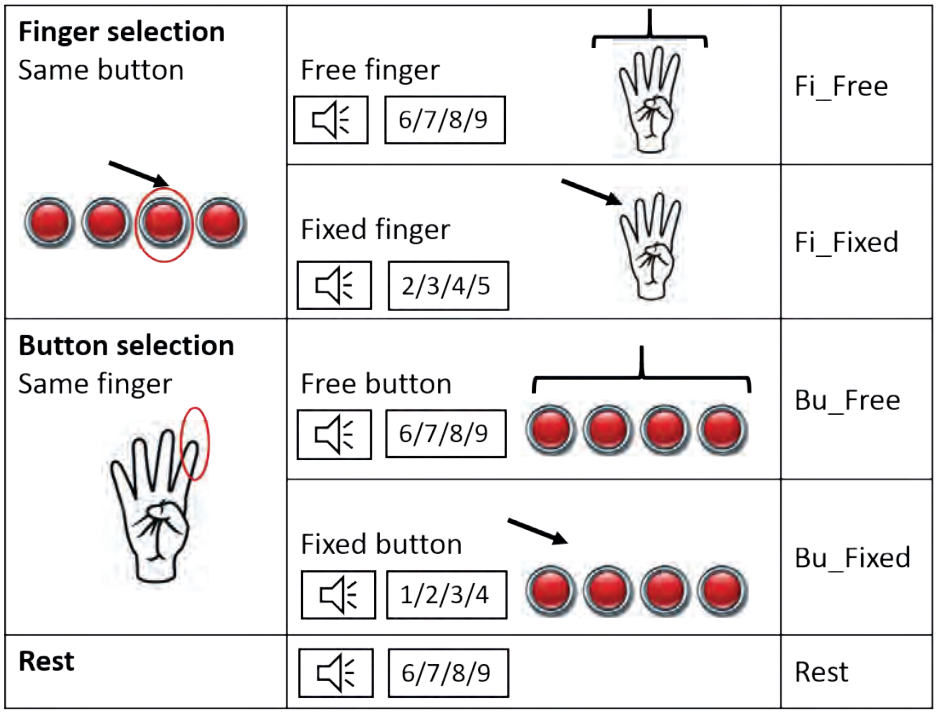


Figure 1. Conditions of the block paradigm. Blocks were alternated, each block contained 8 stimuli and blocks were repeated 16 times in total.

Each condition contained 8 stimuli, and was repeated 16 times, resulting in 128 stimuli per condition, divided over 2 runs of 18 minutes in duration. The order of these conditions was organized such a way that each condition was preceded as often by each other condition, using pseudo-randomization by means of a magic square. The paradigm was designed and run in Presentation software (Neuro Behavioural Systems, Inc. Albany CA).

fMRI recording and set-up

The scans were recorded with a 3 Tesla MRI scanner (Philips Medical Systems, Best, the Netherlands), with a 32-channel SENSE head coil. An axial T1-weighted 3D turbo field echo (T1TFE) sequence image was made for anatomical reference: TR 9 ms; TE 3.5 ms; number of echoes 1; flip angle 8°; matrix size = 256 x 256; FOV: 232 x 170 x 256 mm; voxel size 1 x 1 x 1 mm; acquisition time: 4 minutes 18 seconds. Functional imaging was acquired with a gradient-echo T2* blood oxygen level-dependent contrast technique, with a TR (time repetition) of 2000 msec and a

TE (time echo) of 28 msec. 37 slices and 550 volumes per run were acquired. Images were tilted in the anterior commissure-posterior commissure plane, flip angle 70°. Patients were instructed to lay as still as possible. For auditory instructions, MR-compatible electrodynamic headphones were used (MR Confon GmbH, Magdeburg, Germany). Subjects were able to see their right hand via a double mirror, and with minimal effort could reach a 4-button response box (fORP, Current Designs, Inc. Philadelphia, PA).

Data Analyis

Task performance

Response times were compared between groups using t-test, using the means of single subjects for each condition per run. Response time was measured from the beginning of the stimulus to the recorded response.

fMRI analysis

We used statistic parametric mapping software for fMRI data analysis (SPM12, Wellcome Department, University College London, London, UK). Preprocessing consisted of realignment to the mean image and co-registration to T1-weighted anatomical image of the participants. Normalization was done using the EPI Montreal Neurological Institute (MNI) template provided in SPM12 and spatial smoothing with an 8 mm full-width at half maximum Gaussian kernel.

First level analysis was performed in which all 4 experimental conditions were contrasted to the rest condition at subject level using 1-sample t-tests. Framewise displacement was calculated from the motion parameters and added to the model.

At second level a flexible factorial design was used for results at group level. Contrast between conditions were made one-on-one (for example free finger versus fixed finger selection) and combined (for example all free (both finger free and button free) versus all fixed (both finger fixed and button fixed) conditions). In this respect the combination of Fi_Free and Bu_Free is referred to as 'all free', Fi_Fixed and Bu_Fixed is 'all fixed', Fi_Free and Fi_Fixed is 'all fingers', Bu_Free and Bu_Fixed is 'all buttons'. A combination of all conditions compared to rest is referred to as 'all motor'.

Initially these contrast were made in the healthy control group only, to replicate our previous study. Then, contrasts at subject level were compared between groups (both Patients > Controls, and Controls> patients).

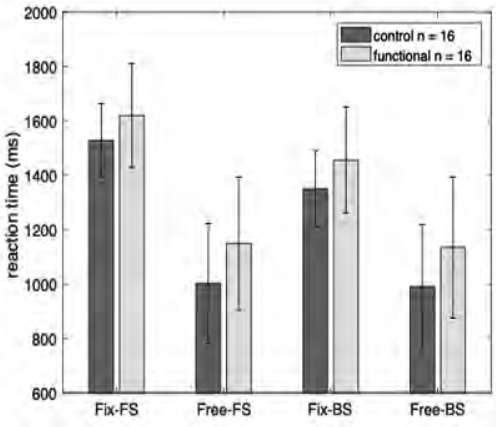
In this second level design, conditions were assumed to be dependent, while subjects were considered independent. The resulting set of maps for the different contrasts were thresholded: Clusters of increased activation within the cortex were considered statistically significant at $p < 0.001$; threshold (k) of 20 voxels (uncorrected), following Woo et al [20].

Post hoc, four crucial activated regions were selected for further investigation, originating from the second level contrasts . These were selected based on hypothesis, focusing mainly on parietal and frontal regions derived from our previous study [16], supplemented with regions that are known to be involved in FMD from meta-analysis [13]. These regions, annotated as 'regions of interest (ROI)', were used for connectivity analyses and correlations with symptom severity.

Connectivity analyses were performed using generalized PPI (psychophysiological interactions). For this PPI analysis, an Automated toolbox for a generalized form of psychophysiological interactions (GPPI), was used [21].

Symptom severity, as measured on the CGI, was correlated to the beta values extracted from the ROIs, using Spearman's rho (one-tailed).

RESULTS



Supplementary figure 1. Response times for every condition in patients and controls. No significant differences between groups were found.

Task performance

Patients showed consistently slower reaction times, which were not specific for one of the conditions and did not significantly differ between groups (see supplementary Fig.1 for details). The pattern of reaction times between conditions is highly comparable to our previous paper [16].

fMRI results

1. Contrasts of conditions within the healthy control group

The contrast of all free compared to all fixed conditions in healthy controls, showed predominantly bilateral involvement of antero-superior prefrontal and bilateral parietal activations, of which the latter particularly resulted from the comparison of free finger versus fixed finger selection. The reverse contrast of fixed vs free conditions showed involvement of the extrastriate visual cortex and activation along the dorsal intraparietal sulcus. In healthy controls, all finger (both free and fixed) conditions versus all button selection (free and fixed), showed activations of the occipital and anterior parietal cortices, including the postcentral sulcus. The reverse contrast, all button versus all finger selection, did not result in significant differences of cortical activations. Figure 2 summarizes these findings. The results were highly comparable to the results found in our previous paper [16].

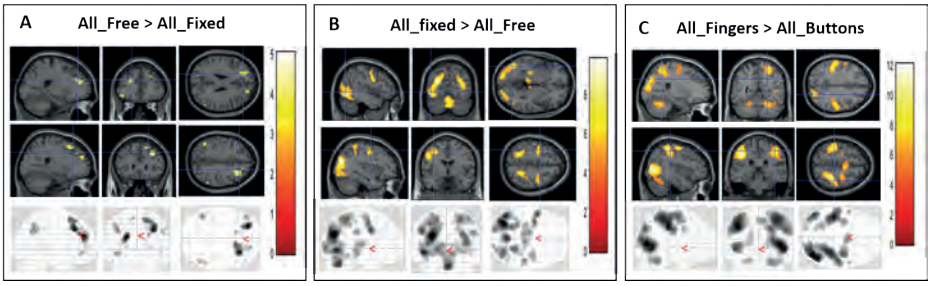


Figure2. Contrasts of conditions within healthy controls. A: All free vs all Fixed conditions show activations in the prefrontal cortex bilaterally, B: All fixed over all free conditions show activation of the occipital lobes bilaterally and in the interparietal sulcus. C: All fingers over all buttons showing activations in the occipital and parietal lobe, including the postcentral sulcus. The fourth contrast, all buttons over all fingers did not result in significant cortical activations. D: p<0.001 uncorrected, A+C: p<0.05 FWE-corrected.

2. Contrasts of conditions in FMD compared to healthy controls

2A) All motor conditions versus rest

The conjunction of all motor conditions compared to the rest condition revealed that patients had significantly reduced activity of the left primary motor cortex (M1) and left premotor cortex (P<0.05 FWE corrected). See Table 1 and Fig.3A. Contrasting the four motor conditions separately to rest, showed a small area of reduced activation

in patients in the same part of the primary motor cortex (M1). No other differences in activations were found in this contrast, nor in the opposite contrast (patient-related increases over controls).

2B) Contrasts between motor conditions

In general, patients showed task specific regional decreases of activation in a coherent distribution of distinct parietal regions, when compared to controls. In addition, regional changes were seen which are specified below. All findings are summarized in figure 3 and table 1.

Free selection versus Fixed instruction

In all free over all fixed conditions patients had less activation in the left angular gyrus, i.e. the infero-posterior parietal cortex ($p<0.001$ uncorr.) compared to controls.

Fixed instruction versus Free selection

In the contrast of fixed over free finger selection (Fi_fixed>Fi_Free), there was a larger difference in FMD patients compared to controls in the left insula (Fig.3C).

Contrasting fixed button versus free button selection, there was less activation in patients than in controls in the right parietal operculum, i.e. the infero-anterior parietal cortex (Fig.3D), and additional small foci in the left temporal cortex and the right auditory cortex ($p<0.001$ uncorrected) (see table 1).

In the comparison between fixed finger and free finger selection, there was reduced activation in the left premotor area ($p<0.001$ uncorr.) ((Fig.3B) in patients compared to controls.

The conjunction of all fixed conditions compared to all free conditions, the same patient-related reduction of activation, compared to controls, was found in the right parietal operculum and left premotor area. Furthermore, superior parietal activation along the intraparietal sulcus (Fig.3E) was found to be reduced in patients compared to controls.

Finger selection versus Button selection

In the contrast of free finger selection compared to free button selection, there was a significant difference in the left insula. In patients there was higher activation in button than finger selection, in controls there was a higher activation in finger than button selection (Fig.3C). The right anterior cingulate cortex showed a pattern in

which patients had less activation in the finger free condition compared to the button free condition, while controls showed the opposite pattern (Fi_Free>Bu_Free).

When fixed finger selection was compared to fixed button selection, the right postcentral gyrus (Fig.3F) and the left somatosensory cortex were less activated in patients then controls. In patients, the right dorsal extrastriate visual cortex (dorsal cuneus) revealed lower activations in fixed fingers than fixed buttons, while in controls the opposite pattern (fixed fingers > fixed buttons) occurred.

Contrasting all finger over all button selection tasks, the somatosensory cortex on the right side, the right dorsal extrastriate visual cortex (dorsal cuneus) and the postcentral gyrus revealed less activation in patients than in healthy controls, all of which were found in the above described fixed finger over fixed button contrast as well.

Button selection versus Finger selection

There were no significant changes in activation found in the contrast of buttons over fingers between groups.

Two foci of activation that were observed in the cingulate gyrus and anterior prefrontal cortex were disregarded, because the difference between groups was entirely explained by one strongly deviating value in the control group.

Region	Contrast	Coordinates (MNI)	Cluster size (kE)
All_motor versus rest			
Left M1 (primary motor cortex, BA4)	All conditions > Rest x Patients < Controls*	-40 -22 56	307
	Fi_Fixed>Rest x Patients<Controls	-40 -24 54	23
	Fi_Free>Rest x Patients<Controls	-40 -24 56	21
	Bu_Fixed>Rest x Patients<Controls	-38 -24 56	21
	Bu_Free>Rest x Patients<Controls	-38 -22 56	19
Left premotor cortex (BA6)#	All conditions > Rest x Patients < Controls*	-56 0 40	23
Anterior part of inferior parietal cortex (BA48)	All conditions > Rest x Patients < Controls*	60 -40 24	48
Free versus fixed			
Left insula (BA48)^	Fi_Fixed>Fi_Free x Patients>Controls	-38 -4 24	136
Left angular gyrus of parietal cortex (BA39)	All Free>All fixed x Patients<Controls	-38 -52 32	21
Right parietal operculum (BA 48)	Bu_Fixed>Bu_Free x Patients<Controls	50 -28 30	134
	All_fixed>All_free x Patients<Controls	50 -28 32	42
Along left sup. temporal sulcus, anterior segment (BA 21)	Bu_Fixed>Bu_Free x Patients<Controls	-56 4 -14	28
Right auditory cortex (BA42)	Bu_Fixed>Bu_Free x Patients<Controls	4 20 26	42
Left premotor cortex (BA6)#	Fi_Fixed>Fi_Free x Patients<Controls	-52 4 34	139
	All_Fixed>All_Free x Patients<Controls	-50 2 34	125
Left intraparietal gyrus (Sup. parietal cortex, BA7)	All fixed>All_free x Patients<Controls	-18 -54 50	27
Fingers versus Buttons			
Left insula (BA48)	Fi_Free>Bu_Free in controls and Bu_free>Fi_Free in patients	-36 0 20	83
Left anterior sup. temporal gyrus (BA 22)	Bu_Free>Fi_free x patients > controls	-60 -6 -12	73
Right anterior cingulate (BA32)	Fi_Free>Bu_Free in controls and Bu_Free>Fi_Free in patients	16 48 22	83
Right postcentral gyrus (BA3)	Fi_fixed>Bu_Fixed x patients<controls	40 -34 60	56
	All fingers>all buttons x patients<controls		
Left somatosensory cortex (BA3)	Fi_Fixed>Bu_Fixed x Patients<Controls	-40 -28 44	80
	All fingers>all buttons x Patients<Controls	-42 -26 50	30
Right dorsal extrastriate visual cortex (dorsal cuneus BA19)	Fi_Fixed>Bu_Fixed in controls and Bu_Fixed>Fi_Fixed in patients	20 -82 40	64
	All fingers>all buttons x patients<controls	18 -82 38	29

Table 1. Task-specific activation differences between patients and healthy controls.

Same activation of the left premotor cortex. **^**Same activation of the left insula. IPS = intraparietal sulcus. * p<0.05, FWE-corrected, all others: p<0.001 uncorrected.

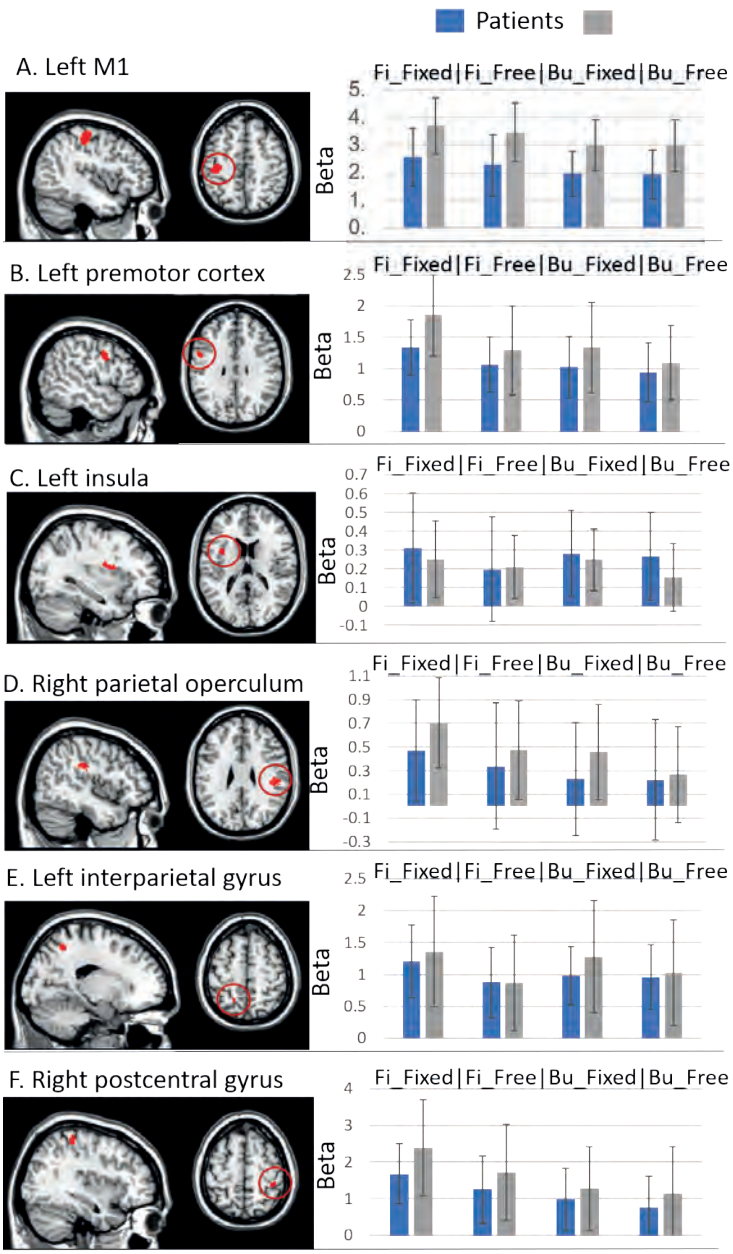


Fig 3. Contrasts of motor conditions between groups. Left: Activation clusters from contrasts between conditions between groups. Right: Beta value of the given cluster in each condition contrasted to the rest condition, per group. A. M1 contrast all motor>rest, pt<co. B. Left premotor cortex, contrasts: all_motor pt<co and fi_fixed>fi_free and all_fixed>all_free. C. Left insula, contrast fi_free>bu_free and fi_free>fi_fixed pt<co. D./E./F. Parietal cortex, respectively: D. Right parietal operculum, Bu_Fixed>Bu_Free , Patients<Controls and all_fixed>all_free; E. Left interparietal gyrus from the contrast All fixed>All_free, Patients<Controls; F. Right postcentral gyrus, Fi_fixed>Bu_Fixed and All fingers>all buttons, patients<controls.

3. Post hoc correlations

Based on the above described activations and the hypothesized involvement of distinct cortical regions, 4 regions of interest (ROIs) were selected for post hoc analysis: 1: The left primary motor cortex (M1), 2: left premotor cortex, 3: the left insula 4: the right parietal operculum (See table 1).

Correlations with symptom severity

We found a significant correlation of symptom severity with reduced activation of the insula in the free finger vs free button contrast, Rho 0.463 (p=0.035) and with the activation of the left premotor area in the fixed finger versus free finger contrast, Rho 0.481 (p=0.030) in patients.

There were no significant correlations between symptom severity and the activations found in the primary motor cortex (p=0.282), and the parietal operculum (p=0.124) and the left insula (p=0.426) in the corresponding contrasts.

Connectivity analysis (PPI)

There was enhanced connectivity in patients over controls of the primary motor cortex with the ventral occipitotemporal cortex (BA37) in the contrast of free finger over fixed finger conditions. The left insula showed reduced connectivity in patients with the superior parietal cortex, extending onto the gyrus postcentralis (- 34 -38 46 = BA 40), the left premotor cortex (- 46 0 30 = BA 6) and along the lateral part of the parieto-occipital sulcus (32 -78 42 = BA 7). There was no difference in connectivity between the left premotor cortex and the rest of the brain. There was reduced connectivity in patients between the right parietal operculum and the bilateral perirhinal cortex/hippocampus in all fixed compared to all free conditions. PPI results are depicted in figure 4.

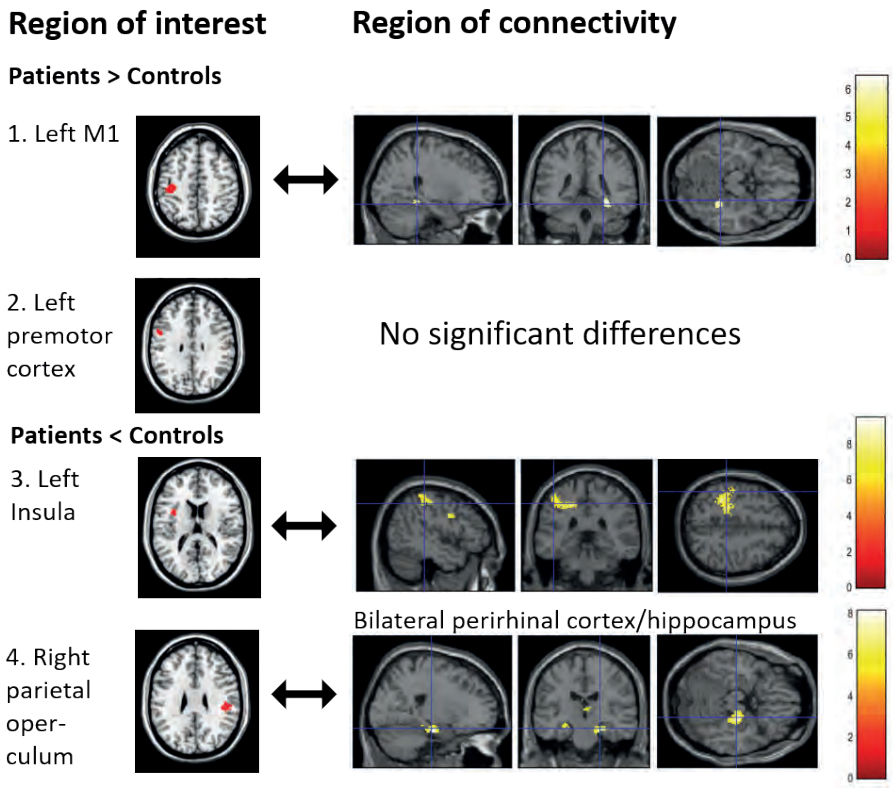


Figure 4. PPI analysis. 1. Enhanced connectivity in patients in Fi_free>Fi_fixed with the occipitotemporal cortex (30 -40 -12, BA37) 2. No significant differences between groups, 3. Reduced connectivity in patients in Fi_free>Fi_fixed with left postcentral gyrus (- 34 -38 46, BA 40) 4. Reduced connectivity in patients in All_fixed>All_free with the bilateral perirhinal cortex/hippocampus (22 -18 -20, BA35). All: P<0.05, FWE-corrected.

DISCUSSION

In this fMRI study of FMD patients and healthy controls, we employed a paradigm comparing selections between either fingers (self-referenced) and buttons (goal-directed), that were either freely chosen (internally cued) or made by fixed instructions (externally cued). In healthy control subjects, the pattern of task-specific fronto-parietal activations replicated previous results [16], with parietal activations along the intraparietal sulcus extending into the post-central sulcus that were dominant in the fixed selection tasks, while activation along the post-central sulcus was particularly related with all finger tasks. This reflected involvement of basic sensorimotor transformations, based on respectively visual and somatosensory information. Parietal activation related to the free selection conditions was particularly seen on

the lateral convexity of the inferior parietal lobe. In FMD patients, reduced activation of premotor and parietal cortices included the left parietal operculum and decreases along the interparietal sulcus in fixed versus free selections, while reduced post-central gyrus and right anterior cingulate activations particularly occurred in self-referenced movement, compared to the goal-directed tasks. An unpredicted main finding was the reduced left primary motor cortex activation in all motor tasks in FMD. Reduced activation of the insula in the contrast of free self-referenced action compared to both fixed self-referenced and free goal-directed action selection in patients, more than in controls, provided novel insight in functional impairment of this region that has often been described in FMD.

The observed FMD-related changes in the fronto-parietal circuitry are consistent with and add to theories on its involvement in motor initiation and voluntary action [2, 22]. In this respect, the coherence between motor intention and mechanisms underlying sensorimotor transformations, that have been found to be particularly maintained by specific parietal regions [23], appears to be affected in FMD. Regarding motor initiation, a contribution of the left angular gyrus has been inferred from switching between motor programs, while the onset of a simple movement element particularly activated the anterior parietal cortex [24]. Consistent with such left hemisphere dominance is the proposed role of the left inferior parietal cortex in motor attention [25]. Moreover, consistent with the concept of 'internal attention' serving motor control, is a left-lateralized parietal involvement in body scheme input to goal-direct movement which can be segregated from the right parietal contribution of an external space representation [26].

Explicit motor control

The overall lower activity of the primary motor cortex and left premotor area in all motor conditions in patients compared to controls might be explained by a difficulty in performing automatic simple motor tasks. Experimental studies have shown a failure of explicit motor control, in which easiest tasks are the most affected in FMD [27, 28] while patients experience most difficult performance with easy, predictable tasks in clinical practice. The slower reaction times in all conditions fit with that explanation. The enhanced connectivity between the primary motor cortex and the ventral occipitotemporal cortex, involved in object recognition, might reflect increased effort of the FMD patients in the simple motor tasks in which an external button is the target to be pushed in all four conditions in patients with FMD.

Sense of agency and body scheme

Arguably, the free finger selection condition implies involvement of both sense of agency (free choice) and body scheme (self-referenced selection), more so than the other conditions in our paradigm. The contrast of the free finger condition with either free button selection or fixed finger selection, yielded reduced left insula activation in FMD patients, which meant that the difference between tasks was stronger in patients than in controls. This relation between free finger selection and the insula thus supports our hypothesis of altered sense of agency and body scheme in FMD. The significant correlation between severity of motor symptoms as measured on the CGI with the insula in one of these contrasts underscores this conclusion, while reduced connectivity of the left postcentral gyrus (somatosensory cortex) and left insula further underlines its relation with an altered perception of body scheme. The insula has indeed been associated with both sensory processing, including the integration of body scheme, and sense of agency [29] and is involved in many neuropsychiatric disorders [30]. It also serves as a network hub that coordinates information across multiple cognitive domains and processes that also include visceral perception and regulation of the autonomic nervous system [31]. Previous studies in FMD have often found altered activity of the insula, both in task-paradigms mostly studying pure motor tasks [32, 33], sense of agency [8] or the interaction between locomotion and emotion [34], and in resting state fMRI [12], including resting state fMRI in non-epileptic attacks [35]. Also, reduced left anterior insular volume was found using voxel-based morphometry in patients with FMD, when stratified for physical health impairment [36]. However, the exact location of differences in the insula varies between studies, as well as the direction of activation compared to healthy controls.

In line with its contribution to sensorimotor transformations, the parietal cortex plays a pivotal role in maintaining a body scheme representation and mediating willed action [7, 37]. Involvement of the parietal cortex, and subsequently the premotor cortex, was found in the contrast between fixed and free action selection. The finding of FMD-related decreases in activation of the left premotor and right parietal operculum in fixed compared to free selections, could be supportive of the hypothesis of reduced sense of agency. Indeed, these regions are involved in functions including visuospatial cognition, imagery of movement and motor preparation, amongst others [25]. The left premotor cortex is specifically associated with selecting movements and is stronger implicated in externally than internally cued action [22], while the opposite holds for the SMA [38]. In this way, the absence of altered activity in the SMA, which was found by Voon et al. [15], may fit the stronger alteration in the

premotor cortex, together with that in the parietal operculum, while it does still underline their conclusion of "potential impairment of prefrontal top-down regulation of motor control to guide action selection". We did not find functional changes in limbic structures.

Some of our results might be interpreted in the light of altered attentional processes, processes that are strongly implicated in reduced sense of agency and altered perception of body scheme. Reduced activation along the posterior part of the intraparietal sulcus (precuneus) in patients when performing the fixed, compared to free conditions, might point at e.g. shifting spatial attention [39] and localizing processes within the internal representation of the body state/ body part [40]. This might be part of a causal mechanism underlying functional impairment in FMD, or could indicate difficulty in allocating attention adequately, inflicted by distraction due to the motor problem. Involvement of the anterior cingulate cortex might similarly be placed in this context. Interestingly it was found reduced in FMD in the fingers over buttons contrast, linking perception of body scheme to decision making.

Apart from the relation between sense of agency and parietal and frontal cortical regions as well as the insula, sense of agency may be seen as deliberate self-attribution of an external event, which is associated with posterior midline structures, mainly the precuneus (i.e. the postero-medial superior cortex) and posterior cingulate cortex [6]. Consistent with such a concept, fixed selection tasks would induce enhanced attention to external cues, with consequent incorporation of such information to match the internal state of the recruited body scheme. This could explain that the observed differences between fixed and free selection seemed to be mainly the result of a relative reduction of activation in the fixed conditions in FMD compared to controls. Even though we had hypothesized to find group differences particularly due to changes in free selection, ie the opposite effect in the same comparison, this unpredicted finding fits with the notion of altered self-attribution associated with abnormal attention towards externally cued movement. In our parallel resting state fMRI study (in the same subjects) using independent component analysis, we found alterations in the low frequency spectra of a component existing of those midline structures associated with self-attribution, namely the (pre)cuneus and a segment of the posterior cingulate cortex (Marapin et al, submitted). The findings in the current study of reduced activity along the intraparietal sulcus, bordering the precuneus, and reduced activity in the right dorsal extrastriate visual cortex in patients neatly complement the resting-state observation. In other words, the functional overlap of these posterior (midline) regions in resting state and

task-evoked imaging highlights a dynamical aspect of a widely distributed network involved in sense of agency and self-attribution within FMD.

The reduced connectivity between the right parietal operculum and the bilateral perirhinal cortex/hippocampus in patients during all fixed conditions, compared to all free, would be consistent with the above proposed concept of self-attributed external events, if one assumes that the specific information in fixed selection introduces potential difficulty in linking such specified information to fitting finger responses.

LIMITATIONS

A number of limitations of the present study need to be considered. We had a relatively small sample size of 16 patients and 16 controls. We chose to display all findings with a threshold of $p<0.001$ uncorrected, which we considered justifiable with our sample size. Also, the reproduction of earlier findings in this new sample and the significant correlation with symptom severity are supportive that our findings are not false-positive.

FMD is a difficult group to study. There is large heterogeneity, in terms of other physical and psychiatric symptoms, intensity and frequency of the movement disorder and a presumed multifactorial etiology. Due to this heterogeneity, it is less likely to find differences between groups. We chose to improve homogeneity by only selecting patients with tremor and myoclonus. Within our sample, depression and anxiety scores were low (comparable to the general population), and therefore our findings could not be attributed to differences between groups on that count.

Within movement disorders, patients' movement during scanning is a general concern. Although we observed patients were lying (perhaps surprisingly) still during the task, we also used frame-wise displacement values within our second level model to correct for movement.

Patients had lower mean reaction times in all conditions. Because we used a block design in which all brain activity within this set time-frame is used, this does not influence the fMRI contrasts. Because this was true for all conditions, it did not influence outcomes of contrasts between conditions.

Generally, experimental setups only partly resemble reality. We aimed to capture 'free selection' (or 'free will') by comparing free choice of a finger or button compared to a instructed finger of button, while timing was specified. However, that is a rather narrow definition of free will. As Haggard [2] pointed out, it is paradoxical to instruct someone to be voluntary. Also, people experienced difficulty with linking the indicated numbers to the different fingers, while this was less difficult in the button condition. Although this was partly overcome by introducing training sessions and did not likely influence differences between groups, it could interfere with the within group comparisons.

CONCLUSION

In this study we identified brain regions implicated in sense of agency and perception of body scheme, of which task-related activations was reduced in FMD. Our data reinforced the association of the insula with both reduced sense of agency and altered perception of body scheme in FMD. Furthermore, reduced activations of premotor and parietal cortices in fixed compared to free action selection further underline the role of a reduced sense of agency, most apparent in response to externally defined tasks. Finally, reduced activation of the primary motor cortex corroborates impaired explicit motor control in FMD.

REFERENCES

1. Edwards MJ, Adams RA, Brown H, Parees I, Friston KJ. A Bayesian account of "hysteria." Brain. 2012;135:3495–512.
2. Haggard P. Human volition: Towards a neuroscience of will. Nat Rev Neurosci. 2008;9:934–46.
3. Salm SMA Van Der, Tijssen MAJ, Koelman JHTM, Rootselaar A Van. The bereitschaftspotential in jerky movement disorders. 2012;:1162–7.
4. Kranick SM, Moore JW, Yusuf N, Martinez VT, Lafaver K, Edwards MJ, et al. Action-effect binding is decreased in motor conversion disorder: Implications for sense of agency. Mov Disord. 2013;28:1110–6.
5. Pareés I, Brown H, Nuruki A, Adams RA, Davare M, Bhatia KP, et al. Loss of sensory attenuation in patients with functional (psychogenic) movement disorders. 2014;:2916–21.
6. Fukushima H, Goto Y, Maeda T, Kato M, Umeda S. Neural substrates for judgment of self-agency in ambiguous situations. PLoS One. 2013;8.
7. Kühn S, Brass M, Haggard P. Feeling in control: Neural correlates of experience of agency. Cortex. 2013;49:1935–42.
8. Nahab FB, Kundu P, Maurer C, Shen Q, Hallett M. Impaired sense of agency in functional movement disorders : An fMRI study. 2017;:8–11.
9. Poppelen, van D, Saifee TA, Schwingenschuh P, Katschnig P, Bhatia KP, Tijssen MA, et al. Attention to self in psychogenic tremor. Mov Disord. 2011.
10. Ricciardi L, Demartini B, Crucianelli L, Edwards MJ, Fotopoulou A. Interoceptive Sensitivity and Sense of Body Ownership in Patients With Functional Neurological Symptoms. J Neurol Neurosurg Psychiatry. 2014;85:e3–e3. doi:10.1136/jnnp-2014-308883.39.
11. Stone J, Gelauff J, Carson A. A "twist in the tale": Altered perception of ankle position in psychogenic dystonia. Mov Disord. 2012;27:585–6.
12. Maurer CW, Epstein SA, Hallett M. Impaired self-agency in functional movement disorders A resting-state fMRI study. 2016;:1–8.
13. Boeckle M, Liegl G, Jank R, Pieh C. Neural correlates of conversion disorder: Overview and meta-analysis of neuroimaging studies on motor conversion disorder. BMC Psychiatry. 2016;16:1–15.
14. Barlas Z, Hockley WE, Obhi SS. Effects of free choice and outcome valence on the sense of agency: evidence from measures of intentional binding and feelings of control. Exp Brain Res. 2018;236:129–39.
15. Voon V, Brezing C, Gallea C, Hallett M. Aberrant Supplementary Motor Complex and Limbic Activity During Motor Preparation in Motor Conversion Disorder. 2011;26:2396–403.
16. Beudel M, De Jong BM. Overlap and segregation in predorsal premotor cortex activations related to free selection of self-referenced and target-based finger movements. Cereb Cortex. 2009;19:2361–71.
17. Pesaran B, Nelson MJ, Andersen RA. Free choice activates a decision circuit between frontal and parietal cortex. Nature. 2008;453:406–9.
18. Jong, de BM. Neurology of widely embedded free will. Cortex. 2011;47:1160–5. doi:10.1016/j.cortex.2011.06.011.
19. Cisek P, Kalaska JF. Neural Mechanisms for Interacting with a World Full of Action Choices. Annu Rev Neurosci. 2010;33:269–98. doi:10.1146/annurev.neuro.051508.135409.
20. Woo C-W, Krishnan A, Wager TD. Cluster-extent based thresholding in fMRI analyses: Pitfalls and recommendations. Neuroimage. 2014;91:412–9.

21. McLaren D, Ries M, Xu G, Johnson S. A Generalized Form of Context-Dependent Psychophysiological Interactions (gPPI): A Comparison to Standard Approaches. Neuroimage. 2012;61:1277–1268.
22. Wise S, Bousaoud D, Johnson P, Caminiti R. Premotor and Parietal Cortex: Coritcocortical Connectivity and Combinatorial Computations. Annu Rev Neurosci. 1997;20:25–42.
23. Andersen R, Buneo C. Intentional maps in posterior parietal cortex. Annu Rev Neurosci. 2002;25:189–220.
24. De Jong BM, Willemsen ATM, Paans AMJ. Brain activation related to the change between bimanual motor programs. Neuroimage. 1999;9:290–7.
25. Rushworth MFS, Johansen-Berg H, Göbel SM, Devlin JT. The left parietal and premotor cortices: Motor attention and selection. Neuroimage. 2003;20 SUPPL. 1.
26. De Jong BM, Van der Graaf FHCE, Paans AMJ. Brain activation related to the representations of external space and body scheme in visuomotor control. Neuroimage. 2001;14:1128–35.
27. Pareés I, Kassavetis P, Saifee T, Sadnicka a, Bhatia K, Fotopoulou a, et al. "Jumping to conclusions" bias in functional movement disorders. 2012. doi:10.1136/jnnp-2011-300982.
28. Pareés I, Kassavetis P, Saifee TA, Sadnicka A, Davare M, Bhatia KP, et al. Failure of explicit movement control in patients with functional motor symptoms. Mov Disord. 2013;28:517–23.
29. Nomi JS, Farrant K, Damaraju E, Rachakonda S, Calhoun VD, Uddin LQ. Dynamic functional network connectivity reveals unique and overlapping profiles of insula subdivisions. Hum Brain Mapp. 2016;37:1770–87.
30. Namkung H, Kim S-H, Sawa A. The Insula: An Underestimated Brain Area in Clinical Neuroscience, Psychiatry, and Neurology: (Trends in Neuroscience 40, 200–207, 2017). Trends Neurosci. 2018;0:200–7. doi:10.1016/j.tins.2018.05.004.
31. Uddin LQ. Salience processing and insular cortical function and dysfunction. Nat Rev Neurosci. 2015;16:55–61. doi:10.1038/nrn3857.
32. Stone J, Zeman A, Simonotto E, Meyer M, Azuma R, Sharpe M. fMRI in motor conversion disorder and simulated weakness. :1–23.
33. van Beilen M, de Jong BM, Gieteling EW, Renken R, Leenders KL. Abnormal parietal function in conversion paresis. PLoS One. 2011;6.
34. Aybek S, Nicholson TR, Zelaya F, O'Daly OG, Craig TJ, David AS, et al. Neural correlates of recall of life events in conversion disorder. JAMA Psychiatry. 2014;71:52–60.
35. van der Kruijs SJM, Bodde NMG, Vaessen MJ, Lazeron RHC, Vonck K, Boon P, et al. Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures. J Neurol Neurosurg Psychiatry. 2012;83:239–47. doi:10.1136/jnnp-2011-300776.
36. Perez DL, Williams B, Matin N, Curt Lafrance W, Costumero-Ramos V, Fricchione GL, et al. Corticolimbic structural alterations linked to health status and trait anxiety in functional neurological disorder. J Neurol Neurosurg Psychiatry. 2017;88:1052–9.
37. Haggard P, Wolpert DM. Disorders of Body Scheme. 2001;:1–7.
38. Passingham RE, Bengtsson SL, Lau HC. Medial frontal cortex: from self-generated action to reflection on one's own performance. Trends Cogn Sci. 2010;14:16–21.
39. Corbetta M, Shulman G, Miezin F, Petersen S. Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. Science (80-). 1995;270:802–5.
40. Frith CD, Blakemore S, Wolp DM. Abnormalities in the awareness and control of action. 2000; April.

Chapter 6.

Altered posterior midline activity in patients with hyperkinetic functional movement disorders, a resting-state fMRI study.

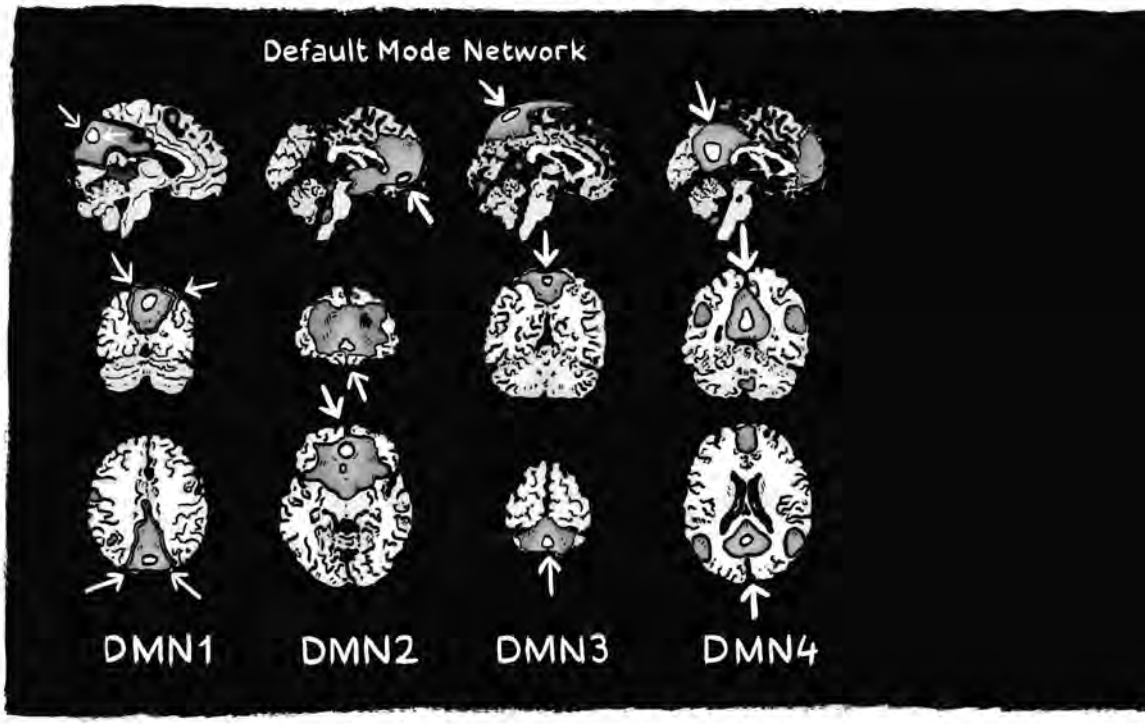
Marapin RS, Gelauff JM, Marsman, JBC, Jong, de BM, Dreissen YEM, Koelman JHTM, Horn, van der HJ, Tijssen MAJ

6. Are there altered activation patterns in a resting-state fMRI experiment in functional motor disorders?

METHODS

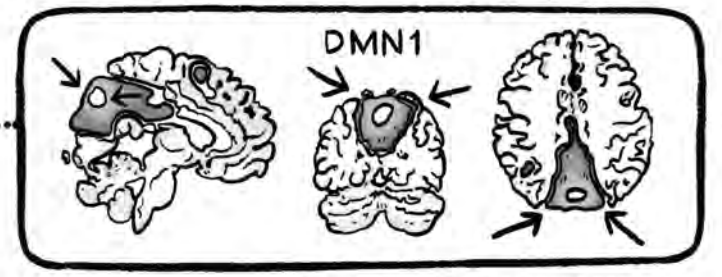
Rest scan fMRI, 2 groups:
17 patients with functional tremor/jerky movements, 17 healthy controls.

A data-driven analysis was performed, in which networks of brain activity (based on connectivity) are generated. From all networks that were generated in both groups, we selected these networks to compare between groups:

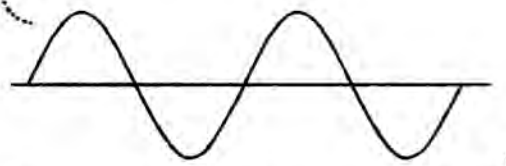


RESULTS

One network showed differences between groups:



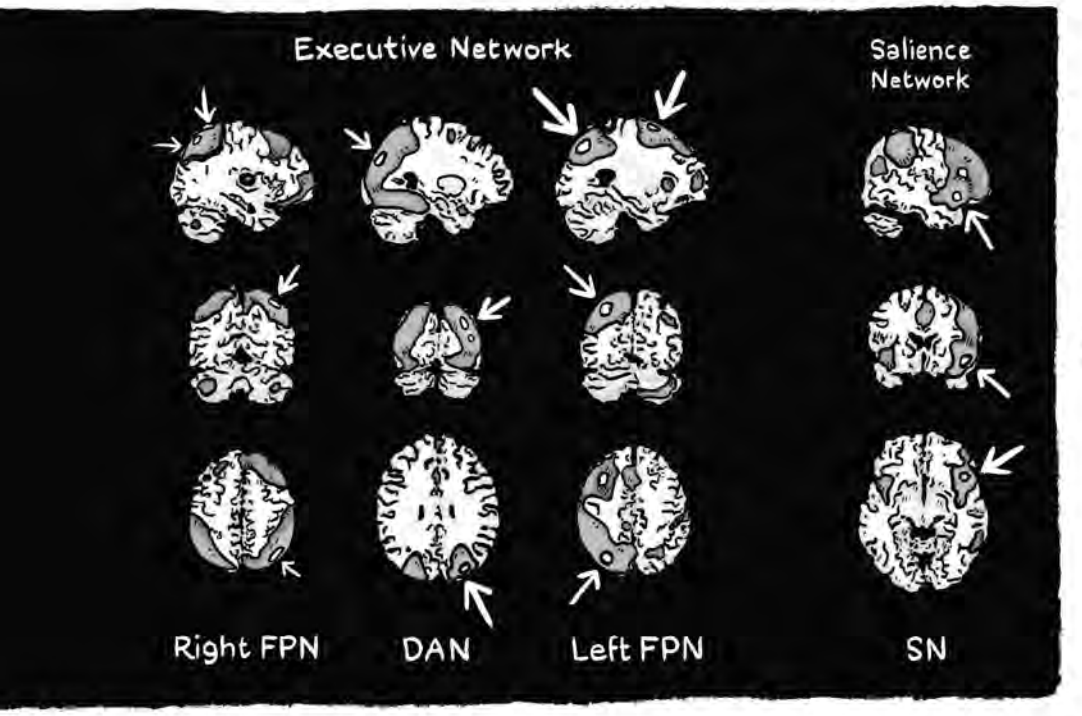
Patients with hFMD exhibit a significantly decreased power of lower-range frequency fluctuations in the precuneus and posterior cingulate cortex network (PCC; FDR-corrected $P<0.05$)



frequencies: 0.068, 0.070, 0.072, 0.074 & 0.076 Hz

No significant group differences were found for intra- and internetwork functional connectivity. In patients with hFMD, symptom severity was not significantly correlated with network measures.

The functional alterations found in this network provide support for the hypothesis that attention is dysregulated in FMD. However, the lack of differences in other networks and measures means there is also large similarity between groups.



ABSTRACT

Objective: To explore changes in resting-state networks in patients with hyperkinetic functional movement disorders (hFMD).

Methods: Resting-state fMRI data from seventeen patients with hFMD and seventeen age-, sex-, and education matched healthy controls was investigated. Independent component analysis was used to examine the central executive network (CEN), salience network (SN), and default mode network (DMN). Frequency distribution of network signal fluctuations, intra- and internetwork functional connectivity were investigated. Symptom severity was measured using the Clinical Global Impression-Severity scale.

Results: Compared with healthy controls, patients with hFMD had significantly decreased power of lower-range (0.01-0.10 Hz) frequency fluctuations in a precuneus and posterior cingulate cortex (PCC) component of the DMN (FDR-corrected $P<0.05$). No significant group differences were found for intra- and internetwork functional connectivity. In patients with hFMD, symptom severity was not significantly correlated with network measures.

Conclusions: The precuneus and PCC contribute to attention shifting, while the precuneus is further known to be involved in parietal circuitry underlying sense of agency. The hFMD-related functional alterations that we demonstrated in these regions therefore provide support for the concept that particularly attentional dysregulation is a fundamental disturbance in these patients.

INTRODUCTION

Functional movement disorders (FMD) represent one of the more common disorders seen in neurological clinics (Stone et al., 2010). Despite its tangible impact, the pathophysiological basis of FMD remains poorly understood.

Recently, Edwards et al. (2012) proposed a Bayesian model which posits that functional symptoms are the result of pathological prior experiences that are modulated by alterations of sense of agency and attention dysregulation. These altered mechanisms are pertinent in patients with FMD as they experience a lack of control over their movements and often direct too much attention towards their body (Hallett, 2010; Pennebaker, 1982). Previous functional neuroimaging studies in FMD support these hypotheses as decreased activation and altered functional connectivity in areas of the right temporoparietal junction (TPJ) and increased activity in the ventromedial prefrontal cortex (vmPFC) were detected (Aybek et al., 2014; de Lange, Roelofs, & Toni, 2007; Maurer et al., 2016; Voon et al., 2010). The TPJ is associated with sense of agency (Decety & Lamm, 2007; Nahab et al., 2011; Ruby & Decety, 2001), while the increased activity found in the vmPFC could reflect heightened self-monitoring in patients with FMD as this region is part of the default mode network (DMN), which is responsible for self-referential processes (Raichle, 2015; Xu, Yuan, & Lei, 2016). Therefore, examining the functioning of brain networks associated with attention and sense of agency in FMD patients can provide valuable insight into the mechanisms underlying FMD.

Resting-state fMRI (rs-fMRI) provides the opportunity to study brain activations in patients while at rest (Biswal, Yetkin, Haughton, & Hyde, 1995). Several rs-fMRI studies have consistently reported the existence of resting-state networks, such as the DMN, a set of brain regions preferentially active when subjects are not engaged in goal-directed behaviors (Damoiseaux et al., 2006; Raichle et al., 2001; Yeo et al., 2011). While most rs-fMRI studies focus on investigating functional connectivity, one can also explore the frequency distribution of blood-oxygen-level dependent (BOLD) signal fluctuations, i.e. assessing distinct frequency bands of such distributed signal fluctuations. A commonly used analysis method includes exploring the power of the lower-range frequency fluctuations (0.01-0.10 Hz), which has been shown to reflect synchronized spontaneous neural activity throughout the brain (Zuo et al., 2010). Investigating this dimension of resting-state functioning is also important, as differences in functioning may not only pertain to patterns of connectivity but also to regional brain activity.

The aim of this study was to explore changes in regional brain activity and functional connectivity within and between networks involved in attention regulation and sense of agency. Therefore, we aimed to study the central executive network(s) (CEN) – consisting of the frontoparietal network (FPN) and dorsal attention network (DAN) –salience network (SN), and DMN in a homogenous population of FMD patients, namely jerky-like (hyperkinetic) functional movement disorders. We used independent component analysis (ICA) to identify resting-state brain networks. This data-driven approach doesn't require an a priori manual selection of regions of interest, but instead finds networks that consist of areas that are functionally independent. We investigated between-group differences in the degree of coherent activity in these networks by analyzing the frequency distribution of network signal fluctuations and in intra- and internetwork functional connectivity. We subsequently assessed whether within-group differences in the frequency distribution of network signal fluctuations and in functional connectivity correlate with symptom severity. To the best of our knowledge, while previous rs-fMRI studies have been done in patients with FMD, no rs-fMRI study has investigated regional brain activity in patients with FMD using the frequency distribution of network signal fluctuations.

METHODS

Participants

Seventeen patients with a clinical diagnosis of hFMD (myoclonus or tremor) were recruited from the movement disorder clinics of the University Medical Center Groningen and the Academic Medical Center, Amsterdam, the Netherlands (Dreissen et al., 2019) . The diagnosis of functional myoclonus or tremor was confirmed by two movement disorder experts (M.T. & J.H.T.M.K.) according to the current DSM-5 criteria using positive findings in the history and neurological examination. Seventeen age-, sex-, and education-matched healthy controls (HC) were recruited via poster ads in the community and the internet.

Exclusion criteria were as follows: age < 18 years; comorbid neurological disorder;; contraindications for MRI-scanning; patients with disruptive jerky movements of the head; and patients using antipsychotic drugs. Of all FMD patients, only one patient was using benzodiazepines at the time and was asked to discontinue their medication one day prior to the scan. Patients were included in a broader study, in which they performed multiple fMRI task paradigms in addition to the rs-fMRI scan and received treatment with botulinum toxin. These results will be analyzed and

reported separately. Patients were scanned between January 2014 and November 2016. All participants in the study provided written informed consent. The study was approved by the medical ethics committee of the Academic Medical Center, Amsterdam, the Netherlands.

Clinical evaluation

Patients with hFMD self-rated symptom severity using the clinical global impression severity (CGI-S) scale, a 7-point Likert-item ranging from 1 to 7 (1 = normal, I have no complaints, 7 = severe). Patients also completed the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988).

MR Imaging acquisition

Functional and structural imaging data were acquired with a 3.0 Tesla MRI scanner (Philips Medical Systems, Best, the Netherlands) using a 32-channel SENSE head coil. Participants lay head-first supine in the scanner. An axial T1-weighted 3D turbo field echo (T1TFE) sequence image was acquired for anatomical reference: TR 9 ms; TE 3.5 ms; number of echoes 1; flip angle 8°; matrix size = 256 x 256; FOV: 232 x 170 x 256 mm; voxel size 1 x 1 x 1 mm; acquisition time: 4 minutes 18 seconds.

With respect to functional imaging, two-hundred twenty-five T2-weighted fast field single echo with echo planar imaging (FEEPI) sequence volumes were acquired, each with 39 slices aligned in the anterior commissure-posterior commissure plane and recorded in descending order: repetition time (TR) 2,000 ms; echo time (TE) 30 ms; flip angle 70°; matrix size = 64 x 62; field of view 224 x 137 x 224 mm; voxel size 3.5 mm x 3.5 mm x 3.5 mm; acquisition time: 7 minutes and 30 seconds. One run was collected per participant. All imaging data was acquired in one session. During the rs-fMRI scan, patients were instructed to remain as still as possible, to keep their eyes open and look in front of them, to remain awake and to think of nothing.

Data preprocessing

We performed rs-fMRI data preprocessing and data analysis following the analytical pipeline shown in Figure 1. Statistical Parametric Mapping (SPM12, version 7219) software was used for fMRI image preprocessing in MATLAB version R2013a. After discarding the first five timepoints of rs-fMRI data for magnetization stabilization, functional images were then realigned to the mean functional image. Six head motion parameters (3 translation and 3 rotation) were calculated during this step and later included in MANCOVA models to control for motion effects. Following co-registration

of the individual T1-weighted image to functional images, images were normalized to the EPI Montreal Neurological Institute template provided in SPM12 software (Calhoun et al., 2017). Finally, the resultant images underwent spatial smoothing with an 8 mm full width at half maximum Gaussian kernel. Images were inspected to ensure proper co-registration and normalization. These images were subsequently used as an input for group ICA.

Data analysis

Preprocessed rs-fMRI data were decomposed into spatially independent components using spatial ICA in the Group ICA of fMRI Toolbox (GIFT, version 3.0b; http://mialab.mrn.org/software/gift/; (Calhoun, Adali, Pearlson, & Pekar, 2001). Spatial ICA entails a data-driven approach which identifies temporally coherent networks by estimating maximally independent spatial sources, referred to as spatial maps, from their linearly mixed fMRI signals, referred to as time courses, and decomposes these into separate components (Allen et al., 2011). Note that "networks" and "components" refer to the same concept in this report. The mean number of independent components was estimated as 24 using the Minimum Description Length criteria (Li et al., 2007). Two-step principal component analysis (PCA) was applied to the group data for dimensionality reduction: 1st step: 38 principal components; 2nd step: 25 principal components. After PCA, group ICA was performed using the FastICA algorithm. The statistical reliability of independent components was assessed using the

ICASSO method that validates the independent components via clustering the results of multiple ICA runs (Himberg, Hyvarinen, & Esposito, 2004); using this method, the component estimation was repeated 20 times.

After group ICA, the Group information guided ICA (GIG-ICA) algorithm (Du et al., 2016; Du & Fan, 2013) in GIFT was performed to generate produce subject-specific images, enabling a comparison of both the time course and the spatial maps to evaluate between-group differences. The GIG-ICA algorithm is a non-data-reduction approach that uses template components (in our case the aggregate component maps from group ICA analysis) as reference to estimate sources of interest for each subject. Subject-specific independent components are computed via a multi-objective function optimization based on the individual-subject data and each remaining non-artifact group-level independent component using a deflation manner. Finally, values of each subject's component image and time course were converted to z-scores. The GIG-ICA method has been shown to achieve better performance than back-

reconstruction (GICA1 and GICA3) and dual regression in aspects of 1) independence of subject specific ICs, 2) accuracy of estimated ICs and time courses (TCs), and 3) spatial correspondence of ICs across subjects (Du & Fan, 2013; Salman et al., 2019). Furthermore, GIG-ICA can remove artifact-related group-level independent components before estimating individual components (Du et al., 2016), therefore only yielding subject-specific meaningful networks.

A validated visual inspection and template matching method was used by authors R.M., J.G., and J.M. to independently and manually select components/networks (Kelly et al., 2010). Components showing spatial overlap with known vascular, ventricular and motion artifacts were excluded. Components corresponding with the DMN, EN and the SN were identified and selected for further analyses.

Network measures

We investigated three ICA-derived outcome measures with respect to network functioning: (1) frequency distribution of network signal fluctuations, denoting the within-network degree of coherent activity; (2) intranetwork functional connectivity, related to the connectivity and degree of coactivation within a network; and (3) internetwork functional connectivity, denoting between-network connectivity. Subject-specific time courses were detrended and despiked using 3dDespike, then filtered using a fifth-order Butterworth low-pass filter with a high frequency cutoff of 0.15 Hz. Furthermore, the six motion parameters calculated during the realignment step were regressed out of the time courses to reduce motion-induced spin history artifacts from the data.

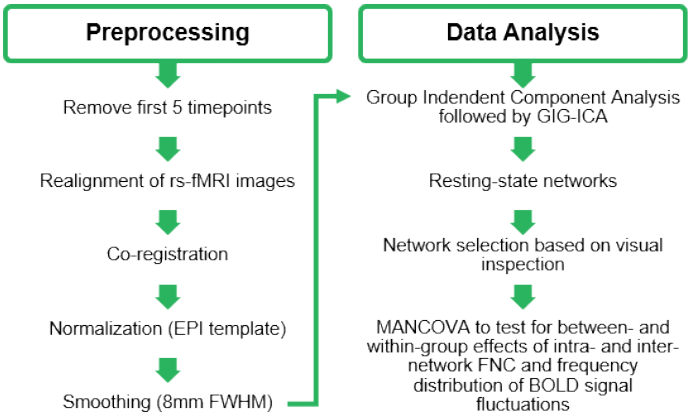
Frequency distribution of network signal fluctuations was estimated on the detrended subject-specific time courses using the multi-taper approach implemented in Chronux. In this paper, fluctuations of frequencies <0.10 Hz and >0.10 Hz will be referred to as lower-range and upper-range frequency fluctuations, respectively. Intranetwork functional connectivity was evaluated using the networks' spatial z-maps. Internetwork functional connectivity was estimated as the Pearson's correlation coefficient between pairs of time courses (Jafri, Pearlson, Stevens, & Calhoun, 2008).

Group analyses

A between-group MANCOVA model was used to test for differences in the frequency distribution of network signal fluctuations and network functional connectivity between patients with hFMD and HC, with inclusion of mean framewise

displacement as a covariate. Framewise displacement is calculated as the sum of the absolute values of the derivatives of the six realignment parameters generated in the preprocessing step (Power, Barnes, Snyder, Schlagger, & Petersen, 2012). Although ICA in and of itself already separates several sources of artefacts, GIG-ICA is especially robust against motion artefacts (Du & Fan, 2013; Murphy, Birn, & Bandettini, 2013). We also regressed out translational and rotational motion parameters and included framewise displacement as a covariate in our statistical models, to correct for any remaining head motion effects (Power et al., 2012). We applied normalizing log-transformations to the continuous variable framewise displacement to improve data symmetry and to reduce disproportionate influence of outliers on the data.

Within-group MANCOVA models were used to test for differences in the frequency distribution of BOLD signals and network functional connectivity between sum scores of CGI-S. Again, log transformed mean framewise displacement was included as a covariate to correct for head motion. The CGI-S scores were not transformed as log-transformation did not improve the data symmetry. Statistical threshold was set at P = 0.05 after correction for multiple comparisons using false discovery rate (FDR; Genovese, Lazar, & Nichols, 2002).



Schematic of the pipeline used in rs-fMRI data preprocessing and data analysis for the investigation of the frequency distribution of BOLD signal fluctuations and functional connectivity. BOLD = blood-oxygen-level dependent; EPI = echoplanar imaging; FMD = functional movement disorders; FWHM = full width at half maximum; HC = healthy controls; MANCOVA = multivariate analysis of covariance; rs-fMRI = resting-state fMRI.

RESULTS

Patient characteristics

Data from 17 patients with hFMD and 17 age-, sex- and education-matched HC were included in the analysis. Patient demographic and clinical characteristics are summarized in Table 1. There were no differences in age, sex and education level between the patient and control groups (P>0.05). The average score of the BDI in patients was 8.2 (SD 7.9), which corresponds to no depression (0-9 out of 63), while the average score for the BAI was 17.2 (SD 13.3), which corresponds to mild anxiety (10-18 out of 63). These psychometric scores are reported with the purpose to demonstrate that there was no clinically significant depression or anxiety in the FMD patients and were not used in the analysis.

	Patients with hFMD (n = 17)	Healthy controls (n= 17)	P-value
Age, mean (SD), years	43.6 (14.4)	43.2 (14.5)	0.93
Sex, females/males	9/8	9/8	1.00
Education level, less than higher professional education	11	7	0.17
CGI-S Score (0-7), mean (SD)	4.8 (1.1)	NA	

Table 1 Patient characteristics Abbreviations: hFMD = hyperkinetic functional movement disorders; CGI-S = clinical global impression-severity scale; NA = not applicable; data are presented as the mean ± SD unless specified otherwise.

Resting-state networks

Group ICA was performed using rs-fMRI data from 34 participants and extracted 24 components. Of these 24 components, eight were selected for further analysis. Spatial maps of the selected resting-state networks are shown in Figure 2. Four components corresponded with parts of the default mode network (DMN1: precuneus, posterior cingulate cortex (PCC); DMN2: medial prefrontal cortex (mPFC); DMN3: precuneus; DMN4: mPFC, PCC and inferior parietal cortex), three components corresponded with the executive network (left and right frontoparietal network; dorsal attention network); one component corresponded with the salience network.

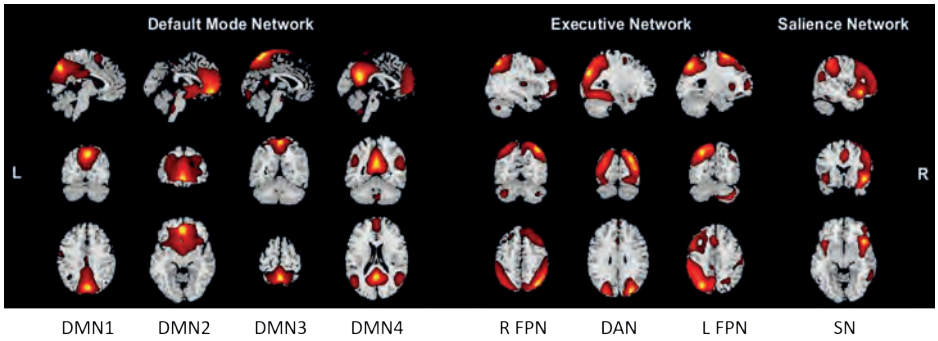
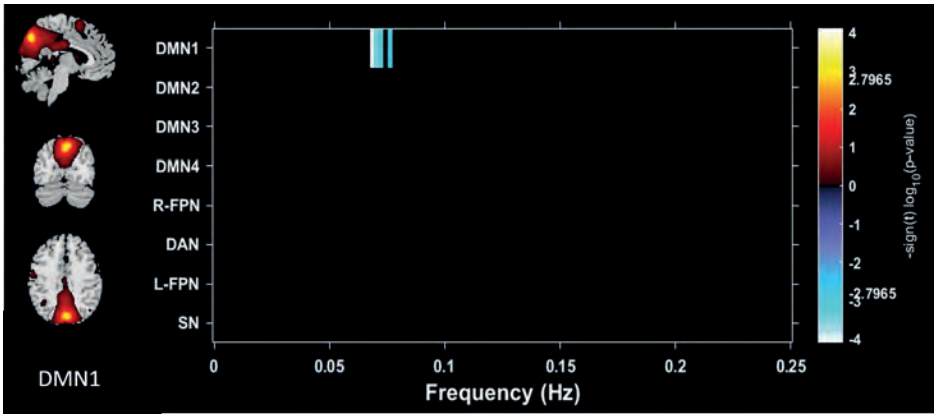


Figure 2. Resting-state networks of interest. Spatial maps of the 8 resting-state networks of interest, where components corresponding to the same network are grouped together. Spatial maps are plotted as *t*-statistics and are displayed at the three most informative slices in the sagittal, coronal and transverse plane. Left side of the figure corresponds with the left side of the brain and vice versa. DAN = dorsal attention network; DMN = default mode network; FPN = frontoparietal network; L = left; R = right.

Frequency distribution of network signal fluctuations analysis

Compared with HC, patients with hFMD exhibited significantly decreased power of lower-range frequency fluctuations in the precuneus and PCC network (DMN 1; Figure 3; FDR-corrected $P<0.05$). The rest of the components did not show significant differences. The frequency distribution of network signal fluctuations in the precuneus and PCC component in patients with hFMD and HC were plotted for comparison purposes (Figure 4). Frequency distribution of network signal fluctuations was not significantly related to CGI-S scores in patients after FDR-correction for multiple comparisons.

A



B

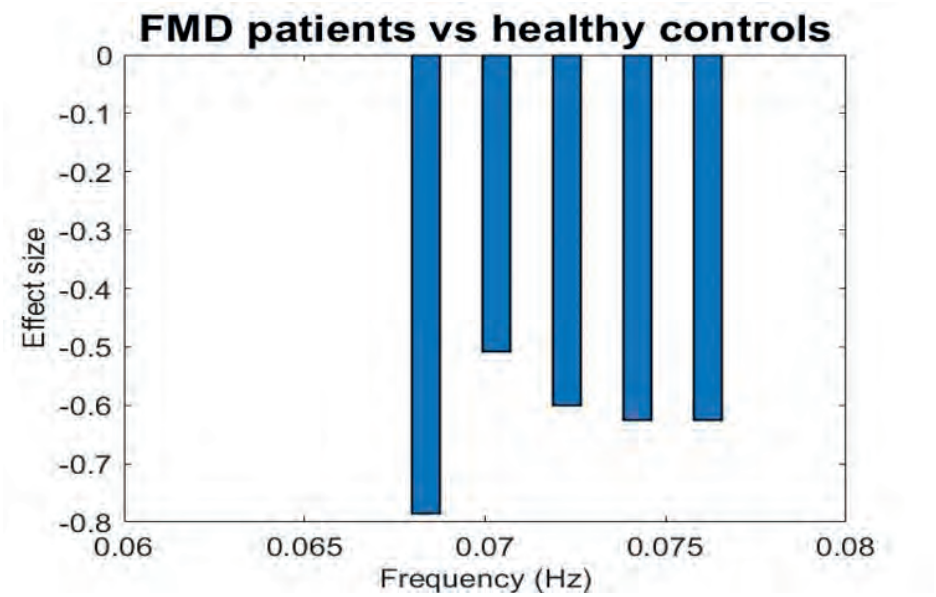


Figure 3. Results of the frequency distribution of network signal fluctuations comparison in patients with hFMD and HC. Figures demonstrate the between-group differences in frequency distribution of network signal fluctuations in patients with hyperkinetic functional movement disorders (hFMD) compared with healthy controls (HC). **(A)** Patients with hFMD exhibit a significantly decreased power of lower-range frequency fluctuations (frequency bins 0.068, 0.070, 0.072, 0.074 & 0.076 Hz) in the precuneus and posterior cingulate cortex network (PCC;FDR-corrected P<0.05). **(B)** Average effect size for each significant frequency. Effects are considered significant if P_{FDR} <0.05.

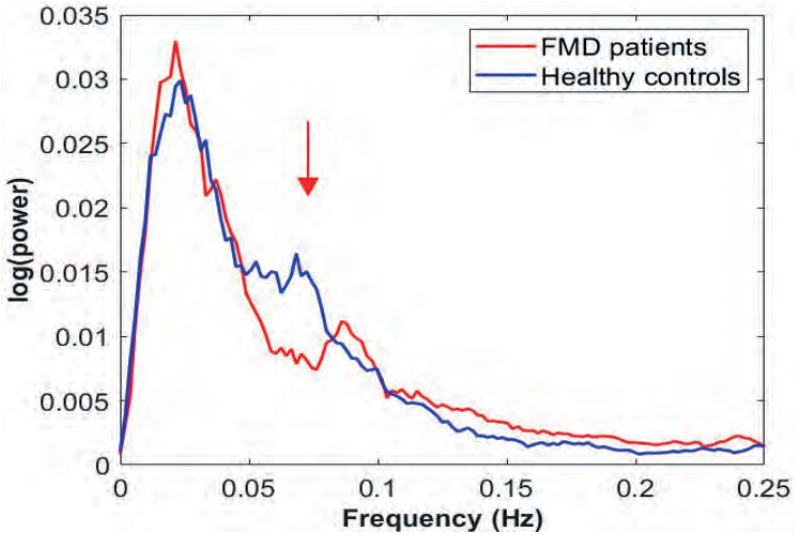


Figure 4. Frequency distribution of network signal fluctuations in the precuneus and PCC component in patients with hFMD and HC. Figure illustrates the differences in frequency distributions of network signal fluctuations in the precuneus and posterior cingulate cortex (PCC) component between patients with hyperkinetic functional movement disorders (hFMD) and healthy controls (HC). Arrows have been included to indicate which frequencies of fluctuations are significantly different: frequency bins 0.068, 0.070, 0.072, 0.074 & 0.076 Hz.

Intranetwork functional connectivity analysis

There were no significant differences in intranetwork functional connectivity in resting-state networks between patients with hFMD and HC after FDR-correction for multiple comparisons. Intranetwork functional connectivity was not significantly related to CGI-S scores in patients after FDR-correction for multiple comparisons.

Internetwork functional connectivity analysis

No significant differences were found in internetwork functional connectivity in resting-state networks between patients with hFMD and HC after FDR-correction for multiple comparisons. Internetwork functional connectivity was not significantly related to CGI-S scores in patients after FDR-correction for multiple comparisons.

DISCUSSION

Currently, the pathophysiological underpinnings of functional movement disorders remain largely unknown. In this study, we aimed to gain further insight in neuronal mechanism underlying FMD by performing a data-driven resting-state fMRI analysis. We found altered regional brain activity in the precuneus and posterior cingulate

cortex (PCC) network in hFMD patients. The precuneus and PCC are known to be involved in attention shifting, while the precuneus is further known to participate in parietal circuitry underlying sense of agency (Cavanna & Trimble, 2006; Farrer & Frith, 2002; Nahab et al., 2011). Therefore, this finding is consistent with the current Bayesian model of FMD as proposed by Edwards et al. (2012). On the other hand, we did not detect any other differences in functional connectivity between groups. Furthermore, symptom severity was not significantly correlated with network measures in patients with hFMD.

Our findings demonstrate decreased power in lower-range frequency fluctuations in the precuneus and posterior cingulate cortex network in patients with hFMD. The precuneus and posterior cingulate cortex networks are considered to be core subcomponents of the default mode network and are associated with attention shifting (Le, Pardo, & Hu, 1998). Altered attentional processing is an important element in the presumed mechanism of hFMD. We know from observation and the experimental set-up of Pareés et al., 2011) that patients' focused attention drives the abnormal motor behavior, and that diverted attention reduces symptoms. The finding of altered activity of the precuneus and posterior cingulate cortex in hFMD is consistent with findings previously described in the literature in patients with FMD. In 2016, Maurer et al. (2016) found altered functional connectivity between the right temporoparietal junction and the right precuneus in patients with FMD. Furthermore, in a task-based fMRI study by Espay et al. (2017) functional dystonia subjects showed areas of decreased activation in the bilateral precuneus. Finally, in a go/no-go task fMRI study with patients with conversion paralysis, the vmPFC (part of the DMN), the posterior cingulate cortex and the precuneus cortex have been found to be hyperactive (Cojan, Waber, Carruzzo, & Vuilleumier, 2009). These task-based analyses confirm the hypothesis that the precuneus is involved in altered attention shifting and motor initiation in FMD. While it should be noted that the functional role of lower-range frequency fluctuations may be novel and relatively unexplored, multiple studies have nevertheless corroborated their importance (Zuo et al., 2010), being vitally involved in the coordination and neuronal organization of brain activity between regions that frequently work in concert (Fox & Raichle, 2007).

We are confident about our findings for the following reasons. First, we implemented a data-driven approach in our study, which eliminates a priori bias in interpreting our findings. Additionally, our results remained significant after being corrected for multiple comparisons using the FDR. Furthermore, we addressed motion artefacts by implementing the ICA method (Murphy et al., 2013), via motion parameter regression,

and including framewise displacement as a covariate in all our regression models (Power et al, 2012). Importantly, we also implemented the GIG-ICA method, which has been shown to yield better performance than existing techniques with respect to independence, spatial correspondence, spatial and temporal accuracy, and motion artifact removal (Du et al., 2016; Du & Fan, 2013). However, while we conclude that our findings may well reflect attention dysregulation, the brain regions found are also associated with other functions, such as episodic memory retrieval (Cavanna & Trimble, 2006). As we did not perform task-based fMRI, we cannot conclude for certain that the alterations found in the precuneus and PCC are directly responsible for the attention dysregulation in FMD, although we consider that most likely given the existing knowledge on FMD in the literature. In this study we found four components which we considered to be part of the DMN, while other studies using the ICA method have reported a different composition of components. For that reason, we argue that attributing too much significance towards the function of networks as a whole, as opposed to individual brain regions, should be dissuaded when interpreting the results.

A significant part of the analyses in our study did not show differences between groups. In this respect it is important to note that our methodology differs significantly from, for example, the study by Maurer et al. (2016) as they used a seed-based approach, while we opted for a data-driven approach using ICA. Additionally, the studies in conversion paralysis and functional dystonia were both task-based fMRI (Cojan et al., 2009; Espay et al., 2017), while we conducted a resting-state based fMRI study. These differences in methodological approaches could explain the lack of changes found in our study with regards to internetwork functional connectivity. Another explanation for the lack of differences between groups in our task-free paradigm could be ascribed to the fact that alterations in brain activity in patients with hFMD might be subtle and specific. This could partly be due to the heterogeneity that is inherent to functional movement disorders in terms of etiological predisposing factors, onset, duration of symptoms and severity of symptoms. The disparity found between studies could be attributed to this same heterogeneity. On the other hand, it is interesting to consider that this is the first rs-fMRI study which analyzed regional brain activity in patients with hFMD, showing alterations in regional brain activity in the absence of impaired functional connectivity. Similarly, McHugo, Rogers, Talati, Woodward, and Heckers (2015) found altered regional brain activity in patients with schizophrenia, whilst the functional connectivity was found to be normal. This could reflect aberrant activity in isolated brain regions and not functional connectivity per se. One may also hypothesize that conventional rs-fMRI analyses focused on

static functional connectivity may fail to identify changes in such interconnections as these functional connections need not be stable over time. This is illustrated e.g. by dynamic rs-fMRI analysis which highlights the dynamic character of state fluctuations (Calhoun, Miller, Pearlson, & Adalı, 2014; van der Horn et al., 2019).

We recognize that our study has a few limitations. First, there was a small sample size (34 participants in total). However, many studies in patients with FMD consist of a sample size smaller than 30 patients. We anticipated the negative effects of a small sample size by limiting our analysis to components that were part of prespecified networks (DMN, EN and SN) to reduce the chance of getting false positive results. However, as a result of that decision we could miss some key findings in networks we did not investigate. Furthermore, our study only included functional myoclonus and tremor, in order to achieve a homogeneous cohort, however, this means that the results are not generalizable to the general spectrum of FMD and are therefore only applicable for this population. Additionally, the lack of a well-validated clinical rating scale for FMD means that we should be cautious when interpreting the association between symptom severity and changes found in this study. Finally, while measures such as duration of symptoms and age of onset were not included as this was beyond the scope of our study, these remain relevant factors to consider when investigating brain functioning in patients with FMD.

While FMD were previously thought to be psychogenic in nature, such a dualistic take on the disorder is now considered unconstructive. In the current study we demonstrated alterations in the precuneus and posterior cingulate cortex, key areas associated with attention shifting which drive abnormal motor behavior in patients with hFMD. Furthermore, the precuneus is also known to participate in parietal circuitry underlying sense of agency. These findings support the concept that particularly attentional dysregulation concerning intended movement and over-attention to its actual execution is a fundamental disturbance in these patients. The lack of differences in internetwork connectivity between groups could be attributed to heterogeneity within hFMD. These findings might contribute to new perspectives and avenues for future studies and to the growing conceptualization of FMD.

REFERENCES

1. Allen, E. A., Erhardt, E. B., Damaraju, E., Gruner, W., Segall, J. M., Silva, R. F., … Calhoun, V. D. (2011). A Baseline for the Multivariate Comparison of Resting-State Networks. *Frontiers in Systems Neuroscience, 5,* 2. https://doi.org/10.3389/fnsys.2011.00002
2. Aybek, S., Nicholson, T. R., Zelaya, F., O'Daly, O. G., Craig, T. J., David, A. S., & Kanaan, R. A. (2014). Neural Correlates of Recall of Life Events in Conversion Disorder. *JAMA Psychiatry, 71(1),* 52. https://doi.org/10.1001/jamapsychiatry.2013.2842
3. Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology, 56(6),* 893-897. https://doi.org/10.1037//0022-006x.56.6.893
4. Beck, A. T. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry, 4(6),* 561. https://doi.org/10.1001/archpsyc.1961.01710120031004
5. Biswal, B. T., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine, 34(4),* 537-541. https://doi.org/10.1002/mrm.1910340409
6. Calhoun, V. D., Adali, T., Pearlson, G. D., & Pekar, J. J. (2001). A method for making group inferences from functional MRI data using independent component analysis. *Human Brain Mapping, 14(3),* 140-151. https://doi.org/10.1002/hbm.1048
7. Calhoun, V., Miller, R., Pearlson, G., & Adalı, T. (2014). The Chronnectome: Time-Varying Connectivity Networks as the Next Frontier in fMRI Data Discovery. *Neuron, 84(2),* 262-274. https://doi.org/10.1016/j.neuron.2014.10.015
8. Calhoun, V. D., Wager, T. D., Krishnan, A., Rosch, K. S., Seymour, K. E., Nebel, M. B., … Kiehl, K. (2017). The impact of T1 versus EPI spatial normalization templates for fMRI data analyses. *Human Brain Mapping, 38(11),* 5331-5342. https://doi.org/10.1002/hbm.23737
9. Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain, 129(3),* 564-583. https://doi.org/10.1093/brain/awl004
10. Cojan, Y., Waber, L., Carruzzo, A., & Vuilleumier, P. (2009). Motor inhibition in hysterical conversion paralysis. *NeuroImage, 47(3),* 1026-1037. https://doi.org/10.1016/j.neuroimage.2009.05.023
11. Damoiseaux, J. S., Rombouts, S. A., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences, 103(37),* 13848-13853. https://doi.org/10.1073/pnas.0601417103
12. De Lange, F., Roelofs, K., & Toni, I. (2007). Increased self-monitoring during imagined movements in conversion paralysis. *Neuropsychologia, 45(9),* 2051-2058. https://doi.org/10.1016/j.neuropsychologia.2007.02.002
13. Decety, J., & Lamm, C. (2007). The Role of the Right Temporoparietal Junction in Social Interaction: How Low-Level Computational Processes Contribute to Meta-Cognition. *The Neuroscientist, 13(6),* 580-593. https://doi.org/10.1177/1073858407304654
14. Dreissen, Y. E., Dijk, J. M., Gelauff, J. M., Zoons, E., Van Poppelen, D., Contarino, M. F., … Tijssen, M. A. (2019). Botulinum neurotoxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomised placebo-controlled trial with an open-label extension. *Journal of Neurology, Neurosurgery & Psychiatry, jnnp-2018-320071.* https://doi.org/10.1136/jnnp-2018-320071
15. Du, Y. H., & Fan, Y. (2013). Group information guided ICA for fMRI data analysis. *Neuroimage, 69,* 157–197. https://doi.org/10.1016/j.neuroimage.2012.11.008

16. Du, Y. H., Allen, E. A., He, H., Sui, J., Wu, L., & Calhoun, V. D. (2016). Artifact removal in the context of group ICA: a comparison of single-subject and group approaches. *Human Brain Mapping, 37,* 1005–1025. https://doi.org/10.1002/hbm.23086

17. Edwards, M. J., Adams, R. A., Brown, H., Parees, I., & Friston, K. J. (2012). A Bayesian account of 'hysteria'. *Brain, 135(11),* 3495-3512. https://doi.org/10.1093/brain/aws129

18. Espay, A. J., Maloney, T., Vannest, J., Norris, M. M., Eliassen, J. C., Neefus, E., … Szaflarski, J. P. (2017). Dysfunction in emotion processing underlies functional (psychogenic) dystonia. *Movement Disorders, 33(1),* 136-145. https://doi.org/10.1002/mds.27217

19. Farrer, C., & Frith, C. (2002). Experiencing Oneself vs Another Person as Being the Cause of an Action: The Neural Correlates of the Experience of Agency. *NeuroImage, 15(3),* 596-603. https:doi/org10.1006/nimg.2001.1009

20. Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience, 8(9),* 700-711. https://doi.org/10.1038/nrn2201

21. Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of Statistical Maps in Functional Neuroimaging Using the False Discovery Rate. *NeuroImage, 15(4),* 870-878. https://doi.org/10.1006/nimg.2001.1037

22. Hallett, M. (2010). Physiology of psychogenic movement disorders. *Journal of Clinical Neuroscience, 17(8),* 959-965. https://doi.org/10.1016/j.jocn.2009.11.021

23. Himberg, J., Hyvarinen, A., & Esposito, F. (2004). Validating the independent components of neuroimaging time series via clustering and visualization. *Neuroimage, 22,* 1214-1222. https://doi.org/10.1016/j.neuroimage.2004.03.027

24. van der Horn, H. J., Vergara, V. M., Espinoza, F. A., Calhoun, V. D., Mayer, A. R., & Naalt, J. (2019). Functional outcome is tied to dynamic brain states after mild to moderate traumatic brain injury. *Human Brain Mapping.* https://doi.org/10.1002/hbm.24827 [Epub ahead of print]

25. Jafri, M. J., Pearlson, G. D., Stevens, M., & Calhoun, V. D. (2008). A method for functional network connectivity among spatially independent resting-state components in schizophrenia. *NeuroImage, 39(4),* 1666-1681. https://doi.org/10.1016/j.neuroimage.2007.11.001

26. Kelly, R. E., Alexopoulos, G. S., Wang, Z., Gunning, F. M., Murphy, C. F., Morimoto, S. S., … Hoptman, M. J. (2010). Visual inspection of independent components: Defining a procedure for artifact removal from fMRI data. *Journal of Neuroscience Methods, 189(2),* 233-245. https://doi.org/10.1016/j.jneumeth.2010.03.028

27. Le, T. H., Pardo, J. V., & Hu, X. (1998). 4 T-fMRI Study of Nonspatial Shifting of Selective Attention: Cerebellar and Parietal Contributions. *Journal of Neurophysiology, 79(3),* 1535-1548. https://doi.org/10.1152/jn.1998.79.3.1535

28. Li, Y. O., Adali, T., & Calhoun, V.D. (2007). Estimating the number of independent components for functional magnetic resonance imaging data. *Human Brain Mapping, 28,* 1251-1266. https://doi.org/10.1002/hbm.20359

29. Maurer, C. W., LaFaver, K., Ameli, R., Epstein, S. A., Hallett, M., & Horovitz, S. G. (2016). Impaired self-agency in functional movement disorders. *Neurology, 10.1212/WNL.0000000000002940.* https://doi.org/10.1212/wnl.0000000000002940

30. McHugo, M., Rogers, B. P., Talati, P., Woodward, N. D., & Heckers, S. (2015). Increased Amplitude of Low Frequency Fluctuations but Normal Hippocampal-Default Mode Network Connectivity in Schizophrenia. *Frontiers in Psychiatry, 6,* 92. https://doi.org/10.3389/fpsyt.2015.00092

31. Murphy, K., Birn, R. M., & Bandettini, P. A. (2013). Resting-state fMRI confounds and cleanup. *NeuroImage, 80,* 349-359. https://doi.org/10.1016/j.neuroimage.2013.04.001

32. Nahab, F. B., Kundu, P., Gallea, C., Kakareka, J., Pursley, R., Pohida, T., ... Hallett, M. (2011). The Neural Processes Underlying Self-Agency. *Cerebral Cortex, 21(1),* 48-55. https://doi.org/10.1093/cercor/bhq059

33. Pareés, I., Saifee, T. A., Kassavetis, P., Kojovic, M., Rubio-Agusti, I., Rothwell, J. C., ... Edwards, M. J. (2011). Believing is perceiving: mismatch between self-report and actigraphy in psychogenic tremor. *Brain, 135(1),* 117-123. https://doi.org/10.1093/brain/awr292

34. Pennebaker, J. W. (1982). The Psychology of Physical Symptoms. https://doi.org/10.1007/978-1-4613-8196-9

35. Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage, 59(3),* 2142-2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

36. Raichle, M. E. (2015). The Brain's Default Mode Network. *Annual Review of Neuroscience, 38(1),* 433-447. https://doi.org/10.1146/annurev-neuro-071013-014030

37. Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, 98(2),* 676-682. https://doi.org/10.1073/pnas.98.2.676

38. Ruby, P. E., & Decety, J. (2001). Effect of subjective perspective taking during simulation of action: a PET investigation of agency. *Nature Neuroscience, 4(5),* 546-550. https://doi.org/10.1038/87510

39. Salman, M. S., Du, Y., Lin, D., Fu, Z., Fedorov, A., Damaraju, E., ... Calhoun, V. D. (2019). Group ICA for identifying biomarkers in schizophrenia: 'Adaptive' networks via spatially constrained ICA show more sensitivity to group differences than spatio-temporal regression. *NeuroImage Clinical, 22,* 101747. https://doi.org/10.1016/j.nicl.2019.101747.

40. Stone, J., Carson, A., Duncan, R., Roberts, R., Warlow, C., Hibberd, C., ... Sharpe, M. (2010). Who is referred to neurology clinics?—The diagnoses made in 3781 new patients. *Clinical Neurology and Neurosurgery, 112(9),* 747-751. https://doi.org/10.1016/j.clineuro.2010.05.011

41. Voon, V., Gallea, C., Hattori, N., Bruno, M., Ekanayake, V., & Hallett, M. (2010). The involuntary nature of conversion disorder. *Neurology, 74(3),* 223-228. https://doi.org/10.1212/wnl.0b013e3181ca00e9

42. Xu, X., Yuan, H., & Lei, X. (2016). Activation and Connectivity within the Default Mode Network Contribute Independently to Future-Oriented Thought. *Scientific Reports, 6(1)*, 1-10. https://doi.org/10.1038/srep21001

43. Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., ... Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology, 106(3),* 1125-1165. https://doi.org/10.1152/jn.00338.2011

44. Zuo, X., Di Martino, A., Kelly, C., Shehzad, Z. E., Gee, D. G., Klein, D. F., ... Milham, M. P. (2010). The oscillating brain: Complex and reliable. *NeuroImage, 49(2),* 1432-1445 https://doi.org/10.1016/j.neuroimage.2009.09.037

Acknowledgements:

Dr. J.M. Gelauff received an unrestricted grant from the graduate school GSMS of the University of Groningen, providing (amongst others) for the costs of this study. Dr. Marina A.J. Tijssen reports grants from the European Fund for Regional Development from the European Union (01492947) and the province of Friesland, ZONMW-TOP (91218013), Dystonia Medical Research Foundation, from Stichting

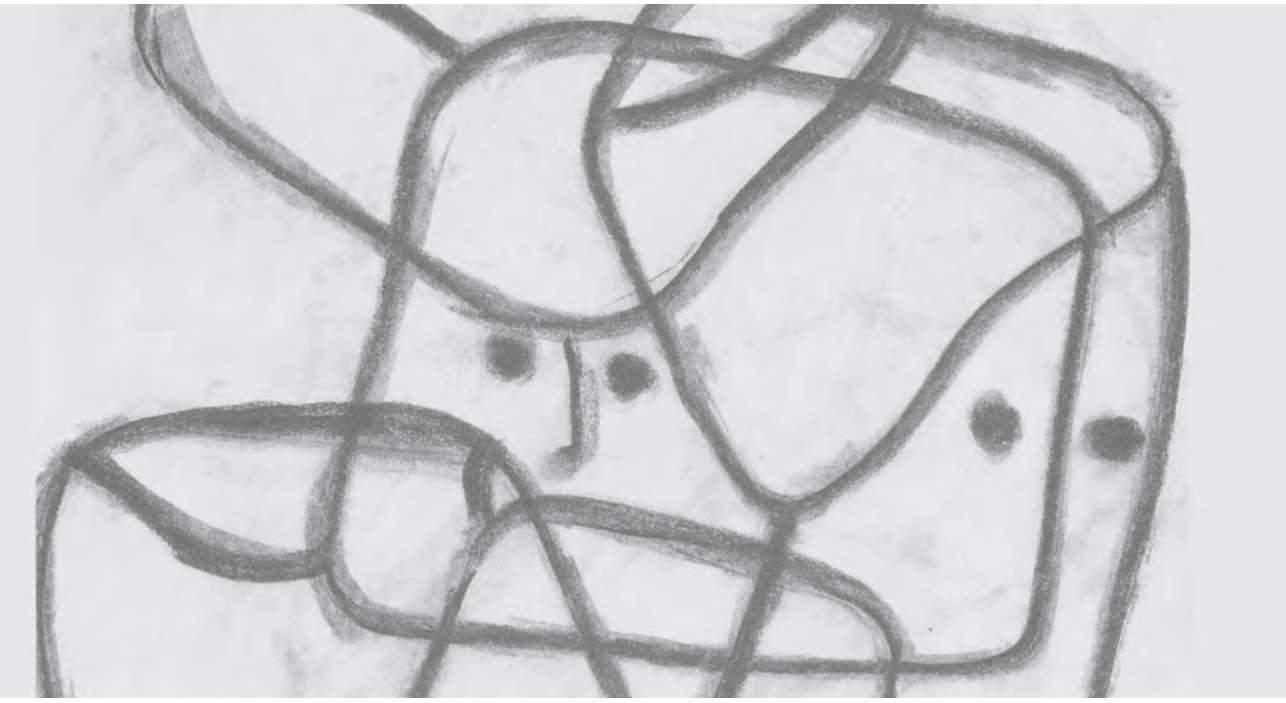
Wetenschapsfonds Dystonie Vereniging, from Fonds Psychische Gezondheid, from Phelps Stichting, and an unrestricted grant from Actelion.

Conflict of Interest Statement:

All authors report no disclosures relevant to the manuscript.

Data availability statement:

The data that support the findings of this study are available on request from the corresponding author.



Part 2. Prognosis

Chapter 7.

The Prognosis of Functional Neurological Disorders.

Gelauff JM, Stone J.

Published as
Book chapter: *Gelauff JM, Stone J, Prognosis of functional neurologic disorders. Handb Clin Neurol 2016, 139, 523-541. Doi: 10.1016/B978-0-12-801772-2.00043-6*
Systematic review: *Gelauff JM, Stone J, Edwards M, Carson A. The Prognosis of Functional (Psychogenic) Motor Symptoms: A Systematic Revie w. J Neurol Neurosurg Psychiatry 2014, 85 (2), 220-6. Doi: 10.1136/jnnp-2013-305321*

ABSTRACT

The prognosis of functional (psychogenic) neurological disorders is important in being able to help answer patient's and carer's questions, determine whether treatment is worthwhile, and to find out which factors predict outcome. We reviewed data on prognosis of functional neurological disorders from two systematic reviews on functional motor disorders and dissociative (non-epileptic) seizures as well as additional studies on functional visual and sensory symptoms.

Methodological problems, include heterogeneity in studied samples and outcome measures, diagnostic suspicion and referral bias, small size and retrospective design of available studies, possible treatments during follow-up and literature review bias.

With these caveats, the prognosis of functional neurological disorders does appear to be generally unfavourable. In a large part of the studies, functional motor symptoms and psychogenic non-epileptic attacks remain the same or are worse in the majority of patients at follow-up. Measures of quality of life and working status were often poor at follow-up. Frequency of misdiagnosis at follow up was as low as other neurological and psychiatric disorders.

Long duration of symptoms was the most distinct negative predictor. Early diagnosis and young age seem to predict good outcome. Emotional disorders and personality disorders were inconsistent predictors. Litigation and state benefits were found to be negative predictors in some studies, but others found they did not influence outcome.

INTRODUCTION

The prognosis of any disorder is important in being able to help answer patient's and carer's common questions about the future, determine whether treatment is worthwhile, and to find out which factors determine poor and good outcome.

Views about prognosis of functional neurological symptoms expressed in the literature are quite markedly variable. Historically the neurologists' view has often swithered towards over optimism, mostly based on the conviction that symptoms that occur without any assignable pathology, should disappear as quickly as they arise. This view has sometimes been confused with an overall treatment approach of some neurologists involving a feeling that they must reassure the patient that they will get better, with the view that doing so will help that outcome to occur.

However, in clinical practice and especially in tertiary centres, neurologists encounter many patients that suffer from chronic, disabling symptoms, resistant to many forms of treatment. Over optimistic views of physicians who treat these patients can discourage both patient and physician in the long run, when symptoms do not resolve. On the other hand too little optimism in a disorder that may be dependent in part on abnormal focused attention and 'habit' may lead to an outcome that is worse than it otherwise might be.

In this chapter, we discuss the prognosis of functional neurological symptoms in adults and children starting with methodological issues, then discussing the data by symptom type, as well as prognostic factors, misdiagnosis and symptom cross-over. We have drawn on data from two systematic reviews, one on motor disorders co-written by the authors of this chapter (Gelauff ***et al.***, 2014), and another on non-epileptic seizures (Durrant, Rickards and Cavanna, 2011). We supplemented this with a further literature search to update these reviews and describe studies of other functional neurological symptoms, especially those older studies where symptoms were grouped together.

We present data of studies with at least eight patients in follow-up, that report on follow-up duration of 3 months or more and in which a majority of patients had functional neurological symptoms.

METHODOLOGICAL ISSUES

There are a number of difficulties in determining overall outcome of functional neurological symptoms, some of which are listed below:

1. *Heterogeneity.* Arguably the only thing that patient with functional neurological disorders really have in common with each other is their symptoms. Some patients have symptoms for a few hours, others for their whole life. Some have complex psychological and physical comorbidity, some present with a single transient symptom. Patients often want to know 'How long will I have this for?'. The studies we have can only hint at the answer to that question. Clinical experience also teaches us that some patients who on paper may have several poor prognostic factors can do surprisingly well, sometimes in relation to non-medical life events such as divorce or a change of job. Patients who theoretically are in the best prognostic group may do surprisingly badly.

2. *Diagnostic Suspicion Bias.* Patients with comorbidities, especially psychological ones, that may predict poor outcome are perhaps more likely to be given a diagnosis of a functional disorder in the first place, thus altering long term outcome.

3. *Secondary and Tertiary Care Referral Bias.* It would be hard to carry out a truly population based study of Functional Neurological Disorders since they usually require diagnosis in secondary care. Patients may be sampled in neurology services, specialist neurology clinics, videotelemetry lists, psychiatry services or tertiary centres draining the most complex patients from a wide area. Many studies described in this chapter were performed in tertiary centres, while a patients that present at an emergency department or at the GP with functional symptoms of short duration probably have a better outlook.

4. *Study size and design*. Many studies are relatively small and potentially prone to the play of chance. Retrospective studies dominate the literature. These are problematic as they are more likely to be non-consecutive and so less representative. Individual studies measure different prognostic factors. Statistical analysis for prognostic factors can sometimes seem more like 'data mining' and may depend on the biases of the authors of the study.

5. *Follow up rates*. Follow up rates in studies range between 50% and 100% with most studies sitting at around 70%. There is an obvious bias here although whether this favours patients with a better outcome or those with a worse outcome is uncertain

6. *Assessing natural history vs treatment studies.* Most of the studies in this chapter describe 'natural history'. However, many of these patients have had treatment which may have confounded the outcome.

7. *Measuring Outcome*. Prognostic and treatment studies and anecdotal experience suggest that patients' wellbeing is not always correlated with improvement of symptoms. Either patients' symptoms have resolved, but quality of life hasn't improved, or vice versa. A study of 147 patients with non-epileptic seizures casts doubt on whether measuring seizure frequency for example, is the most meaningful outcome measure by showing that equal proportions of patients were receiving state related benefit in the 29% who had seizure remission at four years compared to those who still had seizures (Reuber *et al.*, 2005). Outcome may objectively appear better but from the patients perspective be no different. In a study of multidisciplinary inpatient treatment, the objectively rated HoNos was the most sensitive to change over time whereas subjectively rated measures performed less well(Demartini *et al.*, 2014), perhaps because patients have an inherent difficulty in rating themselves accurately (Ricciardi *et al.*, 2015).

8. *Literature review bias.* Most of the data in this chapter comes from a systematic review. Nonetheless there are potentially issues with missing studies especially from non-english sources, and from studies using different terminology. It should be noted that studies that were used in this chapter are heterogeneous in their study approach and numbers of included patients are small, so strong conclusions cannot be drawn.

SYMPTOM OUTCOME

With all of the caveats and potential confounders listed above, the prognosis of functional neurological disorders does appear to be generally unfavourable. Tables 1-3 show data from prognostic studies grouped by symptom type. In a large number of studies symptoms remain-the "same or worse" in the majority of

patients. Producing a meaningful 'bottom line' figure is not really possible due to the above mentioned heterogeneity, including in follow-up duration, follow-up rate and outcome measures. In addition most study designs are retrospective and numbers are generally small.

In recent years research has evolved to categorised studies according to symptom type (e.g. non-epileptic seizures, functional movement disorder) in contrast with earlier studies that looked at 'conversion disorder' or 'hysteria' as a whole. We therefore discuss prognosis by symptom type but also present data from older studies of all functional neurological disorders.

Motor symptoms

We have previously systematically reviewed the prognosis of functional motor symptoms, consisting of movement disorders, paresis and gait disorders(Gelauff *et al.*, 2014). This review covered studies between 1940-2013. We found 24 studies in total (n=2069 patients, two of these studies with overlapping data excluded) where there was follow up data of at least 6 months and there were more than 8 patients reported (Table 1). The functional motor symptoms studied were tremor (n=5 studies), dystonia (n=3 studies), weakness (n=5 studies), parkinsonism (n=1 study) and mixed motor (n=11 studies).

The overall prognosis of motor symptoms appeared unfavourable from the studies in this review. The mean duration of follow-up was 7.4 years. An analysis of all studies weighted according to the size of the study found an overall figure of 40% of patients with the same or worse outcome at follow up, with only 20% of patients with complete remission. In four studies with 135 patients 66% to 100% of patients had the same or worse symptoms at follow-up. In 14 studies with 533 patients, 33% to 66% of patients had the same or worse symptoms at follow-up and in only five studies with 464 patients, 33% or less of patients had symptoms same or worse at follow-up.

The review showed there is variability in outcome between different functional motor symptoms, but no clear relationship between outcome and symptom type was found. Studies in functional dystonia showed worst prognosis; 73% and 78% of patients had the same or worse symptoms- (Schrag *et al.*, 2004; Ibrahim *et al.*, 2009). Functional tremor also has a relatively poor prognosis, with 44-90% of patients the same or worse at follow-up (Ljungberg, 1957; Deuschl *et al.*, 1998; Kim, Pakiam and Lang, 1999; Jankovic, Vuong and Thomas, 2006; McKeon *et al.*, 2009), The outcome of weakness/paralysis seemed to be more favourable. These differences might be

explained by selection bias: many studies of movement disorders (like tremor and dystonia) were performed in tertiary specialised clinics, while limb weakness is more often seen in general neurology clinics. However, Ljungberg, in a single author study which methodologically is still one of the best, even if its 1950s diagnostic certainty is potentially problematic, compared different symptoms within one large (n=381) prospective study. He also found that tremor had the poorest outcome, compared to gait disorder and weakness at 5 years follow-up (Ljungberg, 1957). On the other hand, two other studies (n=69 in follow-up) found no correlation between motor symptom type and outcome(Williams, Ford and Fahn, 1995; Feinstein *et al.*, 2001) .

Two additional articles of functional axial myoclonus and paroxysmal movement disorder were published after the systematic review with 93 patients in follow-up (Ganos *et al.*, 2013; Erro *et al.*, 2014). Their results are in line with above mentioned findings.

Table 1. Study characteristics of follow-up studies in functional motor symptoms. * and ** partly overlapping studies. N= number of patients at follow-up, F-u = follow-up. Follow-up duration in years (y), months (m) or days (d). Follow-up rate in percentages. Age: mean age, measured at onset of symptoms (o), baseline of the study (b) or unknown (-). Symptom duration in years, either measured at baseline of the study or reported as the time between onset en diagnosis 'time to diagnosis' (ttd). Percentage of females in the

Article characteristics							
Author (year)	**Symptom**	**N in f-u**	**F-u duration**	**F-u rate (%)**	**Mean Age (y)**	**Symptom duration (y)**	**Female (%)**
McKeon et al. 2009	Tremor	33	3.2y	53	50 [o]	0.1-15 [b]	70
Jankovic et al. 2006*	Tremor	127	3.4y	60	44 [b]	4,6 [b]	73
Kim et al. 1999	Tremor	10	1.5y	14	41 [b]	4,1 [b]	66
Deuschl et al. 1998	Tremor	16	0.5-8y	64	42 [b]	2,5 [ttd]	80
Carter 1949	Tremor	8	4-6y	80	-	-	-
Ibrahim et al. 2009**	Fixed dystonia	35	7.6 y	73	43 [b]	11,8 [b]	83
Schrag et al. 2004**	Fixed dystonia	69	3.3y	67	30 [b]	5 [b]	83
Lang 1995	Dystonia	8	?	4	35,5 [o]	3,8 [ttd]	72
Erro et al. 2014	Axial myoclonus	76	2,2 y	10	40 [b]	5,9 [b]	51
Lang et al. 1995	Parkinsonism	14	?	100	43 [o]	-	50
Ganos et al. 2013	Mixed Mov Dis	17	2,3 y	65	39 [o]	-	73
Munhoz et al. 2011	Mixed Mov Dis	58	0.5 y	70	39 [o]	-	88
Ertan et al. 2009	Mixed Mov Dis	26	15d-2y	53	*7-70* [o]	4,4 [b]	70
Thomas et al. 2006*	Mixed Mov Dis	122	3.4y	24	43 [b]	4,7 [b]	73
Feinstein et al. 2001	Mixed Mov Dis	42	3.2y	48	45 [b]	-	62
Williams et al. 1995	Mixed Mov Dis	21	1.8y	88	36,5 o	4,9 [ttd]	79
S A Factor et al. 1995	Mixed Mov Dis	20	0-6 y	71	51 -	2,8 [ttd]	60
Stone et al. 2003	Weakness	42	12.5y	70	36 [b]	-	81
Binzer & Kullgren 1998	Weakness	30	3.5y	86	39 [o]	0,2 [b]	60
Knutsson & Martensson 1985	Weakness	25	0.5-9y	100	*19-47* -	1 day – 5 y	76
Brown & Pisetsky 1954	Weakness	10	1-6y	91	26 [b]	-	10
Carter 1949	Weakness	22	4-6y	96	-	-	-
Crimlisk et al. 1998	Mixed Motor	64	5-7y	88	37 [b]	1,5 [ttd]	48
Mace & Trimble 1996	Mixed Motor	31	9.8y	?	?	-	78
Couprie et al. 1995	Mixed Motor	56	4,5y	93	36 [b]	-	64
Gatfield & Guze 1962	Mixed Motor	24	2,5-10y	65	14-67 [b]		83
Ljungberg 1957	Mixed Motor	381	11.9y	?	28,5 [o]	-	65
Total nr of patients in f-u:	1387		**Weighted mean complete remission rate:**				

study, mainly from the baseline population (not at follow-up). Symptom outcome in percentage of patients with improved, same, worse or remitted symptoms at follow-up. Only studies that reported specifically on complete remission were used to calculate the mean weighted complete remission rate. Table partly adopted from the JNNP article: Gelauff et al. 2014.

Symptom outcome				Functioning	
Worse	**Same**	**Improved**	**Complete remission**	**Disability**	**Work**
64			36	40% severe, 24% moderate, 36% mild	-
43		57	0	-	-
30	60	10	0	-	-
25	38	0	37	If symptoms remained: 75% mod and 25% severely impaired	44% retired
0	50	0	50	-	-
31	46	23	0		-
73		19	8	all on allowance	
0	37	38	25		
17	45	16	22	-	-
0	79	7	14	7% moderate, 57% heavy, 36% fully disabled	79% unable to work, 14% early retired, 7% unemployed
18			82	-	-
40		22	38	-	-
-	-	46	-	-	-
22	21	57	0		33% employed, 30% on disability, 4% unemployed
33	24	33	10	-	17% at work, 76% unemployed
14		57	29	27% disabled	27% at work
50		0	50	-	-
69			31	38% limited in moderate activities	30% disability leave
10		27	63	-	57% at work
0	56		44	-	-
10	20	20	50		
4	14	4	78		
38	14	20	28	-	33% at work, 47% health related retirement
44			56		
43		16	41	34%from small restrictions in lifestyle to severely impaired independence, 7% total dependence	
62		-	38		
0	20		80		65% at work, 14% health related pension
		20 %			

Table 2. Study characteristics of follow-up studies in non-epileptic attacks. N= number of patients at follow-up, F-u = follow-up. Follow-up duration in years (y), months (m) or days (d). Follow-up rate in percentages. Age: mean age, measured at onset of symptoms (o), diagnosis (D), baseline of the study (b) or unknown (-). Symptom duration in years, either measured at baseline of the study (b) or reported as the time between onset and diagnosis ˙time to

Non-epileptic attacks						
Article characteristics						
Author year	**N in f-u**	**F-u duration**	**F-u rate (%)**	**Mean Age (y)**	**Symptom duration (y)**	**Female (%)**
Sadan et al. 2015	51	4,6 y	70	27 o	7,8 ttd	71
Duncan et al.2014	188	8,7 y	72	30,5 o	6,7 ttd	75,5
Chen et al. 2012	47	6-9 m	71	-	-	-
Duncan et al. 2011	47	6 m	87	30 o	1,7 ttd	82
Jones et al. 2010	57	4,1 year	26	39 D	6,7 ttd	61
McKenzie et al. 2010	187	6- 12 m	72	38 B	7 ttd	76
An et al. 2010	52	15.7	81	21 o	0.5 ttd	50
Arain et al. 2007	48	3 m	29	30 o	9 ttd	63
Bodde et al. 2007	22	4-7y	96	30 D	7,2 ttd	86
O'Sullivan et al. 2007	38	21 m	76	34 o	1,7-3,8 ttd	61
Carton et al. 2003	78	0,5-7 y	93	23 o	10 ttd	77
Reuber et al. 2003	164	4,1 y	50	27 o	7,7 ttd	79
Selwa et al. 2000	57	19 - 4 y	67	40 -	?	74
Silva et al. 2001	17	0,5 -3 y	100	25 o	9 ttd	70
Ettinger et al. 1999	43	6-9 m	78	34 o	-	91
Jongsma et al. 1999	28	23-67 m	85	31 D		75
Kanner et al. 1999	45	14 m	100	30 b	1,7 b	69
Riaz et al. 1998	15	14 m	60	16 o	17,2 ttd	80
Ramani et al. 1996	21	4,7 y	62	-	-	
Lancman et al. 1993	63	60 m	86	32 o	-	84
Buchanan & Snars 1993 acute/chronic group	50	2,5y / 3,4 y	100	18 / 28	-	72
Walczak et al. 1995	51	16 m	71	36 D	-	84
Kristensen & Alving 1992	22	5,8 y	79	28 D	9 ttd	86
Meierkord et al. 1991	70	1-14 y	64	7 – 71 o	1-20 ttd	78
Lempert & Schmidt 1990	40	24 m	80	38 B	-	64
Total nr of patients in f-u:	1058					
		Weighted mean complete remission rate:				

diagnosis' (ttd). Percentage of females in the study, mainly from the baseline population (not at follow-up). Symptom outcome in percentage of patients with improved, same, worse or remitted symptoms at follow-up. Only studies that reported specifically on complete remission were used to calculate the mean weighted complete remission rate.

Symptom outcome				Disability/Functioning	
Worse (%)	**Same (%)**	**Improved (%)**	**Complete remission (%)**	**Disability (%)**	**Work (%)**
			39	-	-
31,9% attendance with seizures			-	-	22.8% of 114 patients in employment
	62		38	-	-
	36	13	51	-	-
16	35	42	7		
	62		38	Good 11,5%, intermediate 47,5%, poor 36%	23,5% employed (10% at baseline)
-		46	54	-	-
	65		35	-	50% employed at f-u
-	36	32	32	-	-
	84		16	-	-
11	13	48	28	-	--
	71		29	56,4% dependent	40,5% employment or school, 12,4% unemployed, 41.4% retired on health grounds, 4,8% retired on age grounds
	4	56	40	-	-
	77		23	-	-
9	16	56	19	-	-
21	43	11	25	Overall functioning self-rated: 75% improved	No improvement
-		71	29	-	-
13	7	53	27	-	-
5	14		81		Improved in 24%
	75		25	-	-
	42		58	-	-
0	0	65	35		Improved 20 %
-	(2 patients died)		45	-	-
	60		40	-	-
-	42,5	22,5	35	good 3 pts, fair 15, poor 18, very poor 5	28% at work, 42 % out of work
			33%		

Dissociative (non-epileptic) seizures

The prognosis of dissociative (non-epileptic) seizures (DS) has also been subject to a systematic review (Durrant, Rickards and Cavanna, 2011). This review, of 15 studies, suggested the overall prognosis was poor. In eleven studies, 40% or less patients achieve seizure remission in the follow-up period ((Meierkord *et al.*, 1991; Ettinger *et al.*, 1999; Kanner *et al.*, 1999; Selwa *et al.*, 2000; Silva *et al.*, 2001; Carton, Thompson and Duncan, 2003; Reuber *et al.*, 2003; Arain *et al.*, 2007; Bodde *et al.*, 2007; O'Sullivan *et al.*, 2007; McKenzie *et al.*, 2010).

Our own search of the literature found an additional 10 studies both before and after the publication of the Durrant et al review giving a total of 25 studies(Table 2). Looking at these 25 studies (Table 2), 20 found <50% of the patients had completely recovered at follow-up. The total weighted remission rate in non-epileptic seizure studies was 33%. This number is not corrected for follow-up duration or follow-up rate. In the largest study of 260 patients, 19% of patients actually had an increase in the frequency of seizures at a follow-up duration of 6 to 12 months (McKenzie *et al.*, 2010).

However, more promising outcomes have also been reported and it is perhaps useful to look at these studies in more detail to understand why. One study found relatively good outcome in DS (Buchanan and Snars, 1993). They divided patients in two groups: acute (n=18) and chronic (n=32). In the acute group, a very high number of 83% of patients completely recovered after a mean of 2.3 years of follow-up. In the chronic group 38% of eight patients in total remained the same.

Some studies (Walczak et al. 1995; Ramani et al. 1996; An et al. 2010; Duncan et al. 2011) found that greater than 50% of patients improved at follow up. Although some of these can be explained by short duration (Duncan et al. 2011) or young age (An et al. 2010) in other studies this outcome is harder to understand.

Sensory symptoms

Functional sensory symptoms like numbness or paraesthesia are mostly reported in combination with motor symptoms or non-epileptic attacks. Only two studies report specifically on the prognosis of sensory symptoms (Table 3).

Stone et al. carried out 12 year follow up on 42 from 70 baseline patients with weakness, sensory disturbance or both (Stone *et al.*, 2003). At baseline 57% of patients experienced numbness, 48% of patients still reported this symptom 12.5

years later. A high proportion of patients crossed-over from weakness to numbness and vice versa in this study. However, the 45% of patients with solely sensory symptoms at outset had a better outcome on pain, physical and social functioning than patients who complained of weakness.

Another study followed up 26 from 34 patients with unexplained hemisensory disturbance with numbness, tingling, but excluding patients with chronic pain (Toth, 2003). One third of these patients had motor symptoms with heaviness or clumsiness, and other symptoms including intermittent blurring of vision (28%) ipsilateral disturbance of hearing (16%) were also recorded. At 16 months of follow-up in 30 patients, 17% of patients had the same severity of symptoms and 83% of patients' symptoms were completely resolved. A cautious conclusion from this limited amount of data could be that isolated sensory symptoms seem to have a relatively good prognosis, while outcome of sensory symptoms within a broader spectrum of functional neurological symptoms remains undetermined.

Visual symptoms

The prognosis of functional visual symptoms also appears somewhat better than for motor symptoms. Five studies, in 132 patients, have found a frequency of 46-78 % of patients with improved or remitted symptoms at follow-up (Table 3) (Friesen and Mann, 1966; Behrman and Levy, 1970; Kathol *et al.*, 1983; Sletteberg, Bertelsen and Høvding, 1989; Barris, Kaufman and Barberio, 1992) (see table 1c). Follow-up rate in these studies was low, ranging from 20% to 71%.

Hearing loss

Functional hearing loss is rare and literature on the topic is scarce. There are no studies that met our quality demands with respect to number of patients and follow-up duration. Oishi et al. (2009) and Ban et al.(2006) found in 13 patients in total that patients who were diagnosed early and were treated with steroid injections and psychotherapy seemed to have a good prognosis, but follow-up duration was not stated.

Table 3. Study characteristics of follow-up studies in sensory symptoms, visual symptoms and studies with mixed neurological symptoms. N= number of patients at follow-up, F-u = follow-up. Follow-up duration in years (y), months (m) or days (d). Follow-up rate in percentages. Age: mean age, measured at onset of symptoms (o), diagnosis (D), baseline of the study (b) or unknown (-). Symptom duration in years, either measured at baseline of the study or reported as the time between onset en diagnosis 'time to diagnosis' (ttd). Percentage of females in the study, mainly from the baseline population (not at follow-up). Symptom outcome in percentage of patients with improved, same, worse or remitted symptoms at follow-up. Only studies that reported specifically on complete remission were used to calculate the mean weighted complete remission rate. None of the studies reported on work at follow-up.

Article characteristics								**Symptom outcome**				**Disability (%)**
Author (year)	**Symptom**	**N in f-u**	**F-u duration**	**F-u rate (%)**	**Mean Age (y) (b/f-u)**	**Symptom duration (y)**	**Female (%)**	**Worse**	**Same**	**Improved**	**Complete remission**	
Toth 2003	Hemisensory	30	16 m	88	35 -	2 days	74	20		-	80	-
Sletteberg et al. 1989	Visual symptoms	24	7 y	54	24 b	-	72		55		45	
Barris et al. 1992	Visual symptoms	45	-	63	26 -	-	67	22		78		
Kathol et al. 1983	Visual symptoms	42	53 m	53	32 b	-	78		55		45	Living incapacities confounded by other symptoms. 19% visually disabled
Friesen & Mann 1966	Visual symptoms	11	6-32 y	20	-	-	-	54		46		-
Behrman & Levy 1970	Visual symptoms	10	1-4 y	71	-	16 m b	86	40		60		-
Sharpe et al. 2010	Mixed	716	12 m	63	46 b	-	68	19	48	33		-
Carson et al. 2003	Mixed	66	8 m	73	-	-	64	14	41	45		
Kent et al. 1995	Mixed	32	4,5 y	71	42 f-u	-	75		72		28	-
Chandrasekaran et al. 1994	Mixed	38	5y	51	-	-	100		37		63	-
Wig & Mangalwedhe 1982	Mixed	54	5 y	67	-	-	83	7	19	19	54	-

Mixed studies

The largest prospective follow-up study in mixed functional neurological symptoms is a cohort study of 716 patients followed up over a 1 year period from 1144 seen by 41 neurologists across Scotland. (Scottish Neurological Symptoms Study - SNSS) (Sharpe *et al.*, 2010). Patients were included if the neurologist rated their symptoms as 'not at all explained' or 'somewhat explained' by disease. The symptoms included 'conversion disorder' symptoms (sensory and motor symptoms) but also fatigue and pain disorders, and patients who had a neurological disease but the neurologist viewed the symptoms as unexplained by that disease. Poor outcome, defined as unchanged, worse or much worse symptoms, was reported by 67% of the 716 patients at one year follow-up. This study confirmed findings of an earlier study in a comparable population (Carson *et al.*, 2003), that found 54% of 66 patients were the same or worse at follow-up. Some older studies are still relevant. Carter et al (REF!) found relatively favourable results. Apart from the results in paresis and tremor (Table 1) it was reported that 20 out of 24 patients with amnesia recovered completely within one week after hypnosis or suggestion and stayed well in the following 4-6 years. Only one patient relapsed and developed tremor additionally, the others were untraced. From 29 patients with aphonia, 19 remained well at follow-up, while 7 kept losing their voice in stressful circumstances. Three patients with blindness completely recovered after hypnosis.

QUALITY OF LIFE AND FUNCTIONING AT FOLLOW-UP

Persistence of functional symptoms at follow-up is not the only relevant measure for prognosis. Arguably, quality of life (Jones, Reuber and Norman, 2015) and functioning at follow-up provide a better indication of long term outcome of patients suffering from functional neurological symptoms. As Kathol et al.(Kathol *et al.*, 1983) pointed out in their study with visual impairment, the difficulty in interpreting these data is knowing how much of the impairment relates to the specific neurological symptom compared to other comorbidities commonly found in these patients such as pain, fatigue and emotional disorders.

Studies have reported on several different outcome measures but again outcome is generally unfavourable with high percentages of disabled and impaired patients. A study in weakness found 38% of patients were limited in moderate activities at follow up (Stone *et al.*, 2003), another study in tremor reported daily activities were moderately (75%) or markedly (25%) impaired in the patients with same or worse

symptoms (Deuschl *et al.*, 1998). Couprie et al. (Couprie *et al.*, 1995) found 41% of the patients were disabled (grade 2-5 Modified Rankin) at follow-up and 26% still regularly visited a specialist. McKeon et al. (McKeon *et al.*, 2009)found 40% of patients were severely impaired in at least one activity.

In non-epileptic seizures comparable numbers were reported. Lempert & Schmidt (Lempert and Schmidt, 1990) found the impact of psychogenic non-epileptic seizures at 8-39 months of follow-up on daily life was minor in 32% of patients, moderate in 37% and serious in 29% within a sample of 41 patients. One study investigated the outcome on a epilepsy scale and found global measures to be lower than quality of life in a typical epilepsy cohort (Jones *et al.*, 2010). It was found patients had poor physical function, physical symptoms (like energy/fatigue and pain), poor emotional wellbeing and negative health perception. Another study found 36% of patients rated their general quality of life as being poor(McKenzie *et al.*, 2010).

WORKING STATUS

The frequency of patients in work at follow-up also provides a marker of the overall outcome. Several studies report a high rate of patients not working, ranging from 43% to 89% (Binzer and Kullgren, 1998; Crimlisk *et al.*, 1998) and 20% to 47% of patients taking medical retirement who had motor symptoms (Ljungberg, 1957; Crimlisk *et al.*, 1998; Stone *et al.*, 2003). One study in fixed dystonia even found all patients were on disability allowance at follow-up (Schrag *et al.*, 2004). Similar numbers are seen in non-epileptic seizures (Reuber *et al.*, 2003). Two studies in seizures found numbers of patients in work had increased after the follow-up period, but at baseline this number was already very low in both cases (10 % increased to 24% at follow-up in McKenzie et al. (McKenzie *et al.*, 2011), rates increased from 15% at baseline to 23% at follow-up in Duncan et al. (Duncan *et al.*, 2014)). All of these studies suffer from a lack of a control group to gain an understanding both of rates of working in disease controls and also in the general population of similar age and gender.

CROSS-OVER

As patients with functional neurological symptoms often have more than one symptom and having a functional symptom is a risk factor for developing other

functional symptoms, it would be conceivable symptoms might interchange during the follow-up period. Especially in a therapeutic setting this can be cause for concern: if patients recover from the initial symptoms only to develop new functional symptoms, their functional disorder as a whole has not improved. There is not much evidence that symptoms are replaced in such a manner. In motor symptoms for example, many studies looked at comorbid functional symptoms, but non compared follow-up with baseline symptom count (Gelauff *et al.*, 2014).

One study has specifically looked into symptom cross-over in a cohort of 187 patients with psychogenic non-epileptic attacks at an average follow-up duration of 6 to 12 months (McKenzie *et al.*, 2011). A high number of 'unexplained' (functional) symptoms was reported at baseline. At follow-up it was found that the total number of patients with other 'unexplained' (functional) symptoms had increased with 6.4%, but this was not statistically significant. New symptoms were recorded in 23.5% of patients. No correlation was found between recovery from the non-epileptic attacks and an increase in other functional symptoms. Those who continued to have attacks were just as likely to have new MUS as patients who were attack free. Feinstein et al. found 38% of patients developed other physical symptoms at follow-up, in addition to their original abnormal movements (Feinstein *et al.*, 2001). This was not correlated with good outcome of the initial movement disorder. Stone et al. (Stone *et al.*, 2003) found 58% of those who only had sensory symptoms initially went on to develop weakness. These findings generally oppose the idea that cross-over occurs when symptoms resolve, many studies do show a high rate of functional symptoms at follow-up and symptom replacement is undoubtedly a relatively common clinical experience.

PROGNOSTIC FACTORS

In clinical practice, prognostic factors can be useful to guide treatment in individuals. Studies report on several different factors that are correlated with good or bad outcome in prognostic studies. Table 4 summarises studies looking at prognostic factors (see end of this chapter).

Gender

Gender does not influence outcome of functional neurological disorders. In motor symptoms no correlation was found between gender and symptom outcome (Gelauff *et al.*, 2014). In the SNSS cohort no effect of gender was found either (Sharpe *et al.*, 2010). The only two studies in non-epileptic attacks that found a predictive effect of

age were contradicting: one study found a positive predictive effect of male gender (McKenzie *et al.*, 2010), while another found a positive predictive effect of female gender (Meierkord *et al.*, 1991).

Age at onset

As will be discussed in more detail below, prognosis in children with functional symptoms seems to be better than prognosis in adults. Therefore Durrant et al.(2011) concluded that age has a strong effect on outcome. However, studies that only include adults with non-epileptic attacks, general unexplained neurological symptoms and motor symptoms show heterogeneous results.

In the SNSS cohort of unexplained symptoms (n=716) older age predicted poor outcome (Sharpe *et al.*, 2010). Two studies in non-epileptic attacks (n=268) found older age predicted poor outcome (Reuber *et al.*, 2003; An *et al.*, 2010), as did four studies in motor symptoms (n=211) (Mace and Trimble, 1996; Deuschl *et al.*, 1998; Stone *et al.*, 2003; Thomas, Dat Vuong and Jankovic, 2006). Two studies in sensory symptoms found a correlation between age and outcome, but they included both adults and children (Sletteberg, Bertelsen and Høvding, 1989; Barris, Kaufman and Barberio, 1992). Eight studies in motor symptoms (n= 670) (Ljungberg, 1957; Couprie *et al.*, 1995; Williams, Ford and Fahn, 1995; Binzer and Kullgren, 1998; Crimlisk *et al.*, 1998; Feinstein *et al.*, 2001; Ibrahim *et al.*, 2009; Erro *et al.*, 2014) and five studies in non-epileptic attacks (n=410) (Lempert and Schmidt, 1990; Lancman *et al.*, 1993; Carton, Thompson and Duncan, 2003; Arain *et al.*, 2007; Duncan *et al.*, 2014) found no correlation between age and outcome. All in all the effect of age on outcome is not evident from these studies.

Health related benefits

The influence of receiving health related benefits on outcome of functional neurological disorders is subject of speculation. It has been suggested that personal gain from having a functional neurological disorder, like receiving health related benefits, would prevent recovery. It is a somewhat controversial point of view, as it implies personal gain could be an incentive to remain ill which in turn tends to suggest symptoms are under voluntary control. Alternative explanations of a correlation between litigation and/or receiving health related benefits and poor outcome are conceivable. It could be that disease severity leads to unemployment and is therefore indirectly responsible for the poor outcome. Or worry about their financial situation could prevent patients from improving.

Not many prognostic studies have looked at health related benefits as a prognostic factor. Within the SNSS cohort is was found receiving health-related benefits at initial consultation had a negative effect on outcome (Sharpe *et al.*, 2010). McKenzie at al. (McKenzie *et al.*, 2010) (non-epileptic attacks) found that not receiving social payment predicted good outcome. In motor symptoms one study confirms this (Crimlisk *et al.*, 1998), while three other (partly overlapping) studies found no correlation between litigation and outcome (Feinstein *et al.*, 2001; Jankovic, Vuong and Thomas, 2006; Thomas, Dat Vuong and Jankovic, 2006).

Employment and educational status

Other socio-economic factors that have been studied are employment, which was found to be correlated with good outcome in two studies in non-epileptic attacks n=125 (Carton, Thompson and Duncan, 2003; Duncan, Razvi and Mulhern, 2011) or higher educational status/IQ, which has been found to have a positive predictive effect in non-epileptic attacks (Reuber *et al.*, 2003; Arain *et al.*, 2007; McKenzie *et al.*, 2010). However, a higher number of studies with more patients in total in non-epileptic attacks, motor symptoms and mixed symptoms found no correlation between employment or educational status and outcome (see table 3).

Co-morbidity

Comorbidity, both psychiatric and neurological, is high in functional neurological disorders, but the influence of comorbidity on outcome of the presenting symptoms remains unclear.

In one study in functional tremor it was found that any kind of comorbidity, either psychiatric, somatic or functional, was associated with poor outcome (Jankovic, Vuong and Thomas, 2006). In combination with another five studies it was found in a total of 633 patients with motor symptoms that psychiatric comorbidity (anxiety, depression or personality disorders) predicted worse outcome (Ljungberg, 1957; Mace and Trimble, 1996; Binzer and Kullgren, 1998; Feinstein *et al.*, 2001; Ibrahim *et al.*, 2009).

Two studies in non-epileptic attacks (Kanner *et al.*, 1999; McKenzie *et al.*, 2010) and two studies in visual symptoms (Sletteberg, Bertelsen and Høvding, 1989; Barris, Kaufman and Barberio, 1992) found the same relationship between depression and outcome. One study showed that inhibitedness as a personality trait predicted poor outcome (Reuber *et al.*, 2003). Interestingly three studies, two partially overlapping studies in motor symptoms (Jankovic, Vuong and Thomas, 2006; Thomas, Dat Vuong

and Jankovic, 2006) and one study in non-epileptic attacks (Kanner *et al.*, 1999) found depression or anxiety at baseline was correlated with better outcome. This is most probably due to synergistic effect of improvement of the functional disorder and the psychiatric disorder.

Only a few studies investigated the effect of comorbid functional symptoms or 'unexplained symptoms' on outcome, one study found a low somatisation score predicted good outcome (Reuber *et al.*, 2003). Another study found unexplained symptoms other than NES predicted poor outcome (McKenzie *et al.*, 2010), but a study in motor symptoms and one in NES found it had no influence on outcome (Crimlisk *et al.*, 1998; Duncan *et al.*, 2014).

The influence of organic comorbidity on outcome is also indistinct. For example epilepsy alongside non-epileptic attacks was found to predict poor outcome in three studies (Meierkord *et al.*, 1991; Reuber *et al.*, 2003; Duncan *et al.*, 2014), although Duncan et al. (2014) reported attendance with seizures as outcome variable, which could refer to epileptic seizures too. In another study this effect was not found (Lancman *et al.*, 1993). In motor studies conflicting results were reported (Binzer and Kullgren, 1998; Thomas, Dat Vuong and Jankovic, 2006).

Duration of symptoms

Longer duration of symptoms was found to be correlated with negative outcome in many studies. In non-epileptic attacks this association was found in three studies (Lempert and Schmidt, 1990; Selwa *et al.*, 2000; Reuber *et al.*, 2003) and in motor symptoms in five studies (Knutsson and Martensson, 1985; Mace and Trimble, 1996; Feinstein *et al.*, 2001; Jankovic, Vuong and Thomas, 2006; Thomas, Dat Vuong and Jankovic, 2006). Two other studies in motor symptoms did not find an effect of duration of symptoms on outcome (Williams, Ford and Fahn, 1995; Ibrahim *et al.*, 2009). All in all longer duration of symptoms seems to be one of the most consistent negative predictors of outcome in functional neurological disorders. Many explanations for this effect have been proposed, but irrespective of the mechanism it is important to prevent symptoms from becoming chronic.

Early diagnosis and confidence in the diagnosis

In motor symptoms the only predictor that is tested in more than two studies and also correlates consistently with poor outcome is a long duration between start of symptoms and patients receiving a diagnosis (n=307) (Couprie *et al.*, 1995; S. a Factor,

Podskalny and Molho, 1995; Crimlisk *et al.*, 1998; McKeon *et al.*, 2009; Munhoz *et al.*, 2011; Erro *et al.*, 2014).

In non-epileptic attacks only one study found an early diagnosis to be predictive of good outcome (Duncan, Razvi and Mulhern, 2011), while two others did not find any correlation (Meierkord *et al.*, 1991; Lancman *et al.*, 1993).

Also, two partially overlapping studies in motor symptoms (Jankovic, Vuong and Thomas, 2006; Thomas, Dat Vuong and Jankovic, 2006) and 2 studies in non-epileptic attacks (Silva *et al.*, 2001; Carton, Thompson and Duncan, 2003) found confidence in the diagnosis to positively influence prognosis. SNSS found that beliefs about illness were of key importance in predicting outcome (Sharpe *et al.*, 2010). Expectation of non-recovery and non-attribution of symptoms to psychological factors predicted poor outcome.

Crimlisk et al.(2000) showed in 64 patients with unexplained neurological symptoms that the referral pattern is often extensive. After consultation at the National Hospital for Neurology and Neurosurgery in London, 48% were seen by a neurologist, and 27% by another specialist. A total of 42 (66%) had been admitted to hospital (number of admissions ranged from 0 to11). Furthermore 34% of patients had been referred to rheumatologists, general physicians and specialists in infectious diseases, orthopaedics and immunology for their functional symptoms. This referral behaviour can result in iatrogenic damage and undermines understanding and belief of the diagnosis of a functional neurological disorder. Patients who were not referred, had a better change of improvement in this study.

These findings are clinically highly relevant, because they support the idea that an early, tangible, positive diagnosis is essential in the approach of patients with functional neurological disorders. This has been argued in literature (Carton, Thompson and Duncan, 2003; Stone and Carson, 2011).

Table 4. Prognostic factors at baseline predicting outcome. Studies mostly calculated prognostic factors that predict symptom outcome.

		Positive		Negative		No correlation found	
Factor		**Studies**	**Nr of pts**	**Studies**	**Nr of pts**	**Studies**	**Nr of pts**
Young Age	**Motor**	Thomas et al. 2006; Stone et al. 2003; Mace & Trimble 1996; Deuschl et al. 1998	175	-	-	Erro et al. 2014; Ibrahim et al. 2009; Feinstein et al. 2001; Binzer & Kullgren 1998; Crimlisk et al. 1998; Williams et al. 1995; Couprie et al. 1995; Ljungberg 1957	670
	NES	An et al. 2010; Reuber et al. 2003	233		-	Arain et al. 2007; Carton et al. 2003; Lancman et al. 1993; Lempert & Schmidt 1990; Duncan et al. 2014	410
	Mixed	Sharpe et al. 2010	716	-	-	Carson et al. 2003; Chandrasekaran et al. 1994	104
	Sensory	Sletteberg et al. 1989; Barris et al. 1992	74	-	-	-	-
	Total:	**9 studies**	**1198**	**0 studies**	**-**	**15 studies**	**1184**
Female	**Motor**	-		-	-	Erro et al. 2014; Ibrahim et al. 2009; Stone et al. 2003; Binzer & Kullgren 1998; Crimlisk et al. 1998; Williams et al. 1995; Ljungberg 1957	649
	NES	Meierkord et al. 1991	70	McKenzie et al. 2010	187	Arain et al. 2007; Silva et al. 2001; Lempert & Schmidt 1990; Lancman et al. 1993; Duncan et al. 2014	356
	Mixed	-	-			Sharpe et al. 2010; Carson et al. 2003	782
	Total:	**1 study**	**70**	**1 study**	**187**	**14 studies**	**1787**

Early diagnosis	**Motor**	S.A. Factor et al. 1995; Erro et al. 2014; Munhoz et al. 2011; McKeon et al. 2009; Crimlisk et al. 1998; Couprie et al. 1995	307	-	-	-	-
	NES	Duncan et al. 2011	47	-	-	Lancman et al. 1993; Meierkord et al. 1991; Duncan et al. 2014	321
	Mixed	-					
	Total	**7 studies**	**354**	**0 studies**	**-**	**3 studies**	**321**
Positive reaction to diagnosis	**Motor**	Thomas et al. 2006 (believe in treatment outcome)	122				
	NES	Carton et al. 2003 (also: understanding diagnosis), Silva et al. 2001	95	-	-	Ettinger et al. 1999	43
	Total	**3 studies**	**217**			**1 study**	**43**
Patient believe of non-recovery	**Mixed**	-	-	Sharpe et al. 2010	716	-	-
	Total	**0 studies**	**-**		**716**		
Short duration of illness	**Motor**	Thomas et al. 2006; Feinstein et al. 2001; Mace & Trimble 1996; Williams et al. 1995; Knutsson & Martensson 1985	241	-	-	Ibrahim et al. 2009	35
	NES	Selwa et al. 2000; Walczak et al. 1995; Lempert & Schmidt 1990	148	-	-	-	-
	Mixed	-	-	-	-	Chandrasekaran et al. 1994	38
	Total:	**8 studies**	**389**	**0 studies**	**-**	**2 studies**	**73**

Personality disorder	**Motor**	-	-	Binzer & Kullgren 1998; Mace & Trimble 1996; Ljungberg 1957	442	-	-
	NES	-	-	Kanner et al. 1999; Reuber et al. 2003 (trait: inhibitedness)	209	-	-
	Mixed	-	-	Chandrasekaran et al. 1994	38		
	Total:	**1 study**	**164**	**5 studies**	**525**	**0 studies**	**-**
Psychiatric disorder (Axis-1)	**Motor**	Crimlisk et al. 1998, Thomas et al. 2006	186	Ibrahim et al. 2009; Feinstein et al. 2001; Binzer & Kullgren 1998; Mace & Trimble 199)	138	Erro et al. 2014	76
	NES	Bodde et al. 2007; Kanner et al. 1999 (Kanner: single episode of major depression)	76	McKenzie et al. 2010; Walczak et al. 1995; Kanner et al. 1999 (Kanner: recurrent depression)	283	Carton et al. 2003; Silva et al. 2001; Ettinger et al. 1999; Lancman et al. 1993; Meierkord et al. 1991; Duncan et al. 2014	459
	Mixed	-	-	Sharpe et al. 2010	716	Carson et al. 2003	66
	Sensory	-	-	Barris et al. 1992	45	-	-
	Total	**3 studies**	**140**	**9 studies**	**1182**	**8 studies**	**601**
Somatoform disorder	**Motor**	-	-	-	-	Ibrahim 2009, Crimlisk 1998	99
Other MUS/ Func Symp	**Nes**	McKenzie et al. 2010	187	-	-	Kanner et al. 1999; Lempert & Schmidt 1990; Duncan et al. 2014	273
	Total:	**1 study**	**187**	**0 studies**	**-**	**5 studies**	**372**
Somatic diagnosis	**Motor**	Thomas et al. 2006	122	Binzer & Kullgren 1998	30	-	-
	NES	-	-	Reuber et al. 2003; Meierkord et al. 1991; Duncan et al. 2014	442	Lancman et al. 1993	63
	Mixed	-	-	Sharpe et al. 2010	716	-	-
	Total	**1 study**	**122**	**5 studies**	**1188**	**1 study**	**63**

Disability	**Motor**	-	-	-	-	Thomas et al. 2006; Binzer & Kullgren 1998	152
	NES	-	-	-	-	-	-
	Mixed	-	-	-	-	Carson et al. 2003	66
	Total	**0 studies**	**-**	**0 studies**	**-**	**3 studies**	**218**
Litigation / Benefits	**Motor**	-	-	Crimlisk et al. 1998	64	Thomas et al. 2006; Feinstein et al. 2001	164
	NES	-	-	McKenzie et al. 2010; Ettinger et al. 1999	230	Duncan et al. 2014	188
	Mixed	-	-	Sharpe et al. 2010	716	-	-
	Total	**0 studies**	**-**	**4 studies**	**1010**	**3 studies**	**352**
High level Education/ IQ	**Motor**	-	-	-	-	Feinstein et al. 2001; Binzer & Kullgren 1998; Williams et al. 1995; Ljungberg 1957	474
	NES	McKenzie et al. 2010; Arain et al. 2007; Reuber et al. 2003	399	-	-	Kanner et al. 1999	45
	Mixed	-	-	-	-	Chandrasekaran et al. 1994	38
	Total	**3 studies**	**399**	**0 studies**	**-**	**6 studies**	**557**
Employ-ment	**Motor**	-	-	-	-	Feinstein et al. 2001	42
	NES	Duncan et al. 2011; Carton et al. 2003	125	-	-	Arain et al. 2007; Ettinger et al. 1999; Duncan et al. 2014	279
	Total:	**2 studies**	**125**	**-**	**-**	**4 studies**	**321**
Marital status	**Motor**	Crimlisk et al. 1998 (Change in marital status)	64	-	-	Feinstein et al. 2001	42
	NES	-	-	-	-	Arain et al. 2007	48
	Total	**1 study**	**64**	**0 studies**	**-**	**2 studies**	**90**
Social background	**Motor**	-	-	-	-	Crimlisk et al. 1998	64
	NES	Ettinger et al. 1999 (having many friends)	43	-	-	Reuber et al. 2003; Silva et al. 2001; Lancman et al. 1993	244
	Total	**1 study**	**43**	**0 studies**	**-**	**4 studies**	**308**

Misdiagnosis

Both patients and physicians can remain unconvinced of the diagnostic certainty of functional neurological disorders. They think symptoms that are diagnosed as being a functional neurological disorder often prove to be part of neurological disease eventually. In medical literature this concern has been strongly influenced by one paper on prognosis in which a misdiagnosis rate of more than 50% at 10 years follow-up was found in patients with hysteria (Slater and Glithero, 1965). Based on these findings the author concluded that the concept of hysteria as a syndrome 'was based entirely on tradition and lacked evidential support' (Slater, 1965).

However, Stone et al. (Stone, 2005) have shown in their systematic review on misdiagnosis that included 27 studies and 1466 patients with motor and seizure conversion disorder that since the 1970s the rate of misdiagnosis of functional symptoms has only been 4%(Adler *et al.*, 2014). This is similar to the rate of misdiagnosis for other neurological and psychiatric disorders (Figure 1) There was no difference between motor symptoms (4%) and seizures (2.6%) overall. There was some suggestion that movement disorders and gait disorders specifically were more prone to error. the higher rate of misdiagnosis seen in earlier studies such as Slater appears to relate more to poorly defined cohorts and outcomes than clearly worse diagnosis. The data is compatible with a view that functional neurological disorders are a clinical bedside diagnosis that has been reliably made since before CT scans and videotelemetry.

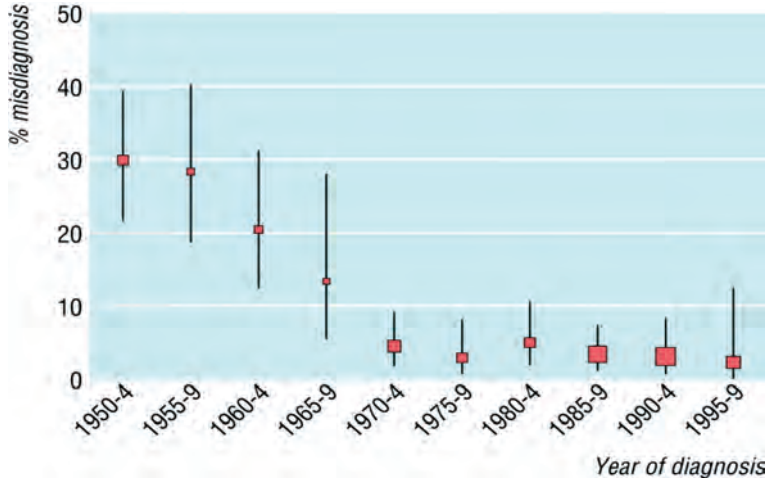


Figure 1. Misdiagnosis of functional neurological disorders (mean %, 95% confidence intervals, random effects) plotted at midpoint of five year intervals according to when patients were diagnosed. Size of each point is proportional to number of subjects at each time point (total n=1466, 27 studies). Reproduced with permission from BMJ publications (Stone, 2005)

Within a prospective large sample of patients (N=1030 followed up from 1144) with unexplained neurological symptoms from the Scottish Neurological Symptom Study, it was found that after 1 year and 7 months of follow-up only four patients acquired a diagnosis of new organic disease that was unexpected at initial assessment and provided a better explanation for the symptoms(Stone *et al.*, 2009). In movement disorders a comparable low rate of zero to three percent was found in 195 patients (Jankovic, Vuong and Thomas, 2006; Ibrahim *et al.*, 2009; McKeon *et al.*, 2009).

One of the reasons for discrepancy between these recent findings and early findings is the interpretation of the definition of misdiagnosis. A change of diagnosis at follow-up does not necessarily explain the original symptoms better, it could simply mean narrowing of the differential diagnosis, a difference in opinion between the initial neurologist and the subsequent physician or a co-morbid neurological diagnosis that does not account for earlier symptoms, but might explain symptoms at follow-up. Earlier studies did not take these subtleties into account(Stone *et al.*, 2009).

Misdiagnosis is a pitfall in many neurological disorders but undoubtedly physicians have traditionally been more worried to miss an organic diagnosis than a functional disorder, although the consequences for the patient are considerable in both situations.

Paediatric studies

On average, children with a functional neurological disorder seem to have a better prognosis than adults with the same symptoms.

Although numbers of patients are low, paediatric studies in non-epileptic attacks show relatively high percentages of completely remitted symptoms. Reilly et al.(Reilly *et al.*, 2013) reviewed the available literature on NES in children and found remission rate ranges from 43 to 81 percent in studies with 15 to 50 patients in follow-up. The proportion of patients with improved or remitted symptoms, 71 to 100%, is impressive compared to the numbers in adults (Durrant, Rickards and Cavanna, 2011; Reilly *et al.*, 2013). It is hypothesized perhaps the shorter duration of symptoms at presentation or possibly more effective local treatment interventions could explain this difference, but no evidence is available.

In a one year follow-up study with motor symptoms, sensory symptoms and/or non-epileptic attacks 75 to 100% of 147 children (median age 12,5 years) had improved symptoms (Ani *et al.*, 2013). In this study motor symptoms and non- epileptic attacks

had a more favourable outcome (90-100% improved) than sensory symptoms like visual loss, hearing loss, speech problems and paraesthesia. Many of these children received some kind of psychotherapy. Despite the favourable outcome for the neurological symptom, a quarter of the children developed a new psychiatric disorder during follow-up, especially anxiety and depressive disorders. Another paediatric study of mixed functional neurological symptoms reported outcome of 30 children that were seen at the emergency department with relatively short duration of symptoms. Symptoms were resolved at follow-up of 3-6 months in 83% of cases (De Gusmão *et al.*, 2014). Despite this, patients on average missed 22.3 days of school, parents missed 8 days of work and patients visited the emergency department twice during the follow-up period. In a study of 15 children with functional movement disorder followed up of 3.1 years, 12 had substantially improved or remitted symptoms. The three children that did not recover, remained highly disabled (Schwingenschuh *et al.*, 2008). Another study summarized findings of outcome in visual symptoms in childhood. In their own series of 58 patients and in the existing literature, outcome was good, with almost all patients completely recovered (Toldo *et al.*, 2010).

Prognostic factors in paediatric studies that correlated with bad outcome are longer duration of symptoms before diagnosis (Pehlivantürk and Unal, 2002; Schwingenschuh *et al.*, 2008), and premorbid conduct problems (such as behaviour that expressed disrespectfulness, difficulty to get along, arrogance or aggression) (Pehlivantürk and Unal, 2002). Comorbid neurological disease (such as epilepsy) was found to be correlated with poor outcome in some but not all studies (Durrant, Rickards and Cavanna, 2011).

CONCLUSION

There are many methodological problems in studying the prognosis of functional neurological disorders but in general they appear to have a poor prognosis with low remission rates at follow-up. Patients with pure sensory symptoms and paediatric populations appear to have a better outcome, although numbers are low. In non-epileptic attacks and motor symptoms differences between symptoms remain unclear.

High frequency of psychological and physical comorbidity is typically reported at baseline and follow-up. From the small number of studies that looked into cross-over at follow-up there was no obvious indication that symptoms get replaced by

other symptoms after they have resolved but this is an unresolved epidemiological question. Perhaps unsurprisingly quality of life, general functioning and working status at follow-up is often found to be low in many cases.

The most consisent negative prognostic factor is long duration of symptoms. Psychiatric comorbidity was not looked at in many different studies, but was found to be an inconsistent predictor of poor outcome. The effect of other comorbidities on outcome remains uncertain. The effect of age is highly dependent on the population. Paediatric studies have shown better outcome than adult studies, so age is clearly predictive of outcome. But within the adult population varying results were found. Socio-economic factors including health related benefits were too variable to draw a conclusion but may be relevant. Gender does not influence outcome. A larger studies with multivariate regression suggest the relevance of illness beliefs in particular.

REFERENCES

Adler, C. H. *et al.* (2014) 'Low clinical diagnostic accuracy of early vs advanced Parkinson disease: Clinicopathologic study', *Neurology*, 83, pp. 406–412. doi: 10.1212/WNL.0000000000000641.

An, D. *et al.* (2010) 'Clinical features of psychogenic nonepileptic seizures: a study of 64 cases in southwest China.', *Epilepsy & behavior : E&B*. Elsevier Inc., 17(3), pp. 408–11. doi: 10.1016/j.yebeh.2010.01.003.

Ani, C. *et al.* (2013) 'Incidence and 12-month outcome of non-transient childhood conversion disorder in the UK and Ireland', *British Journal of Psychiatry*, 202(6), pp. 413–418. doi: 10.1192/bjp.bp.112.116707.

Arain, A. M. *et al.* (2007) 'Predictors of early seizure remission after diagnosis of psychogenic nonepileptic seizures', *Epilepsy and Behavior*, 11, pp. 409–412. doi: 10.1016/j.yebeh.2007.07.017.

Ban, J. H. and Jin, S. M. (2006) 'A clinical analysis of psychogenic sudden deafness', *Otolaryngology - Head and Neck Surgery*, 134, pp. 970–974. doi: 10.1016/j.otohns.2005.11.045.

Barris, M. C., Kaufman, D. I. and Barberio, D. (1992) 'Visual impairment in hysteria', *Doc. Ophthalmol.* Department of Internal Medicine (Division of Visual Science, Michigan State University, East Lansing, 82(0012-4486 SB-IM), pp. 369–382.

Behrman, J. and Levy, R. (1970) 'Neurophysiological studies on patients with hysterical disturbances of vision.', *Journal of psychosomatic research*, 14, pp. 187–194. doi: 10.1016/0022-3999(70)90029-2.

Binzer, M. and Kullgren, G. (1998) 'Motor conversion disorder. A prospective 2- to 5-year follow-up study.', *Psychosomatics*, 39, pp. 519–527. doi: 10.1016/S0033-3182(98)71284-8.

Bodde, N. M. G. *et al.* (2007) 'Factors involved in the long-term prognosis of psychogenic nonepileptic seizures', *Journal of Psychosomatic Research*, 62, pp. 545–551. doi: 10.1016/j.jpsychores.2006.11.015.

Brown, W. and Pisetsky, J. (1954) 'Sociopsychologic factors in hysterical paraplegia', *J.Nerv. Ment.Dis.*, 119, pp. 283–298.

Buchanan, N. and Snars, J. (1993) 'Pseudoseizures (non epileptic attack disorder)--clinical management and outcome in 50 patients.', *Seizure : the journal of the British Epilepsy Association*, 2, pp. 141–146. doi: 10.1016/S1059-1311(05)80119-0.

Carson, A. J. *et al.* (2003) 'The outcome of neurology outpatients with medically unexplained symptoms: a prospective cohort study', *Journal of Neurology, Neurosurgery & Psychiatry*. BMJ Publishing Group Ltd, 74(7), pp. 897–900.

Carter, A. B. (1949) 'The prognosis of certain hysterical symptoms', *BMJ*, i, pp. 1076–1079.

Carton, S., Thompson, P. J. and Duncan, J. S. (2003) 'Non-epileptic seizures: patients' understanding and reaction to the diagnosis and impact on outcome', *Seizure : the journal of the British Epilepsy Association*, 12, pp. 287–294.

Chandrasekaran, R. *et al.* (1994) 'Hysterical neurosis: A follow-up study', *Acta psychiatrica scandinavica*, 89(9), pp. 78–80.

Chen, D. K. *et al.* (2012) 'Intact vs. impaired ictal sensorium: Does it affect outcome of psychogenic nonepileptic events following disclosure of diagnosis?', *Epilepsy and Behavior*. Elsevier B.V., 24(1), pp. 30–35. doi: 10.1016/j.yebeh.2012.03.009.

Couprie, W. *et al.* (1995) 'Outcome in conversion disorder: A follow up study', *Journal of Neurology Neurosurgery and Psychiatry*, 58(6), pp. 750–752. doi: 10.1136/jnnp.58.6.750.

Crimlisk, H. L. *et al.* (1998) 'Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms', *BMJ : British Medical Journal*, 316(February), pp. 582–586.

Crimlisk, H. L. *et al.* (2000) 'Patterns of referral in patients with medically unexplained motor symptoms', *Journal of Psychosomatic Research*, 49, pp. 217–219. doi: 10.1016/S0022-3999(00)00167-7.

Demartini, B. *et al.* (2014) 'Multidisciplinary treatment for functional neurological symptoms: a prospective study', *Journal of Neurology*, 261(12), pp. 2370–2377. doi: 10.1007/s00415-014-7495-4.

Deuschl, G. *et al.* (1998) 'Diagnostic and pathophysiological aspects of psychogenic tremors', *Movement Disorders*, 13, pp. 294–302. doi: 10.1002/mds.870130216.

Duncan, R. *et al.* (2014) 'Primary and secondary care attendance, anticonvulsant and antidepressant use and psychiatric contact 5-10 years after diagnosis in 188 patients with psychogenic non-epileptic seizures.', *Journal of neurology, neurosurgery, and psychiatry*, 85(9), pp. 954–8. doi: 10.1136/jnnp-2013-306671.

Duncan, R., Razvi, S. and Mulhern, S. (2011) 'Newly presenting psychogenic nonepileptic seizures: Incidence, population characteristics, and early outcome from a prospective audit of a first seizure clinic', *Epilepsy and Behavior*. Elsevier Inc., 20(2), pp. 308–311. doi: 10.1016/j.yebeh.2010.10.022.

Durrant, J., Rickards, H. and Cavanna, A. E. (2011) 'Prognosis and Outcome Predictors in Psychogenic Nonepileptic Seizures', *Epilepsy Research and Treatment*, 2011, pp. 1–7. doi: 10.1155/2011/274736.

Erro, R. *et al.* (2014) 'Psychogenic axial myoclonus: Clinical features and long-term outcome', *Parkinsonism and Related Disorders*. Elsevier Ltd, 20(6), pp. 596–599. doi: 10.1016/j.parkreldis.2014.02.026.

Ertan, S. *et al.* (2009) 'Clinical characteristics of 49 patients with psychogenic movement disorders in a tertiary clinic in Turkey', *Movement Disorders*, 24(5), pp. 759–762. doi: 10.1002/mds.22114.

Ettinger, a B. *et al.* (1999) 'Predictive factors for outcome of nonepileptic seizures after diagnosis.', *The Journal of neuropsychiatry and clinical neurosciences*, 11, pp. 458–463.

Factor, S. A., Podskalny, G. D. and Molho, E. S. (1995) 'Psychogenic movement disorders: frequency, clinical profile, and characteristics.', *Journal of Neurology, Neurosurgery & Psychiatry*, 95, pp. 406–12.

Factor, S. a, Podskalny, G. D. and Molho, E. S. (1995) 'Psychogenic movement disorders: frequency, clinical profile, and characteristics.', *Journal of neurology, neurosurgery, and psychiatry*, 59, pp. 406–412. doi: 10.1136/jnnp.59.4.406.

Feinstein, a *et al.* (2001) 'Psychiatric outcome in patients with a psychogenic movement disorder: a prospective study.', *Neuropsychiatry, neuropsychology, and behavioral neurology*, 14(3), pp. 169–176. doi: 11513100.

Friesen, H. and Mann, W. A. (1966) 'Follow-up study of hysterical amblyopia.', *American journal of ophthalmology*, 62(6), pp. 1106–15.

Ganos, C. *et al.* (2013) 'Psychogenic paroxysmal movement disorders - Clinical features and diagnostic clues.', *Parkinsonism & related disorders*. Elsevier Ltd, 20(1), pp. 41–46. doi: 10.1016/j.parkreldis.2013.09.012.

Gatfield, P. D. and Guze, S. B. (1962) 'Prognosis and differential diagnosis of conversion reactions', *Dis.Nerv.Sys.*, 23, pp. 623–631.

Gelauff, J. *et al.* (2014) 'The prognosis of functional (psychogenic) motor symptoms: a systematic review.', *Journal of neurology, neurosurgery, and psychiatry*, 85(2), pp. 220–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24029543.

De Gusmão, C. M. *et al.* (2014) 'Functional neurological symptom disorders in a pediatric emergency room: Diagnostic accuracy, features, and outcome', *Pediatric Neurology*. Elsevier Inc, 51(2), pp. 233–238. doi: 10.1016/j.pediatrneurol.2014.04.009.

Ibrahim, N. M. *et al.* (2009) 'The prognosis of fixed dystonia: A follow-up study', *Parkinsonism and Related Disorders*. Elsevier Ltd, 15(8), pp. 592–597. doi: 10.1016/j.parkreldis.2009.02.010.

Jankovic, J., Vuong, K. D. and Thomas, M. (2006) 'Psychogenic Tremor : Long-Term Outcome', *CNZ Spectr*, 11, pp. 501–8.

Jones, B., Reuber, M. and Norman, P. (2015) 'Correlates of health-related quality of life in adults with psychogenic nonepileptic seizures : A systematic review', pp. 1–11. doi: 10.1111/epi.13268.

Jones, S. G. *et al.* (2010) 'Clinical characteristics and outcome in patients with psychogenic nonepileptic seizures.', *Psychosomatic medicine*, 72, pp. 487–497. doi: 10.1097/PSY.0b013e3181d96550.

Jongsma, M. J. *et al.* (1999) 'Follow-up of psychogenic, non-epileptic seizures: A pilot study - Experience in a Dutch special centre for epilepsy', *Seizure*, 8, pp. 146–148. doi: 10.1053/seiz.1998.0247.

Kanner, a M. *et al.* (1999) 'Psychiatric and neurologic predictors of psychogenic pseudoseizure outcome.', *Neurology*, 53, pp. 933–938. doi: 10.1212/WNL.53.5.933.

Kathol, R. G. *et al.* (1983) 'Functional visual loss - follow up on 42 cases', *Arch Ophthalmol.*, 101, pp. 729–35.

Kent, D. a, Tomasson, K. and Coryell, W. (1995) 'Course and outcome of conversion and somatization disorders. A four-year follow-up.', *Psychosomatics*. Elsevier, 36(2), pp. 138–144. doi: 10.1016/S0033-3182(95)71683-8.

Kim, Y. J., Pakiam, a S. and Lang, a E. (1999) 'Historical and clinical features of psychogenic tremor: a review of 70 cases.', *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques*, 26(3), pp. 190–195.

Knutsson, E. and Martensson, A. (1985) 'Isokinetic measurements of muscle strength in hysterical paresis', *Electroencephalogr.Clin.Neurophysiol.*, 61(5), pp. 370–374.

Kristensen, O. and Alving, J. (1992) 'Pseudoseizures - risk factors and prognosis', *Acta Neurol Scand*, 85, pp. 177–180.

Lancman, M. E. *et al.* (1993) 'Psychogenic seizures in adults: a longitudinal analysis.', *Seizure : the journal of the British Epilepsy Association*, 2, pp. 281–286. doi: 10.1016/S1059-1311(05)80141-4.

Lang, A. E. (1995) 'Psychogenic dystonia: a review of 18 cases.', *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques*. Department of Medicine, Toronto Hospital, Ontario, Canada, 22(2), pp. 136–43.

Lang, A. E., Koller, W. C. and Fahn, S. (1995) 'Psychogenic parkinsonism.', *ArchNeurol*, 52, pp. 802–10.

Lempert, T. and Schmidt, D. (1990) 'Natural history and outcome of psychogenic seizures: a clinical study in 50 patients', *Journal of Neurology*, 237, pp. 35–38. doi: 10.1007/BF00319665.

Ljungberg, L. (1957) 'Hysteria: a clinical, prognostic and genetic study', *Acta Psychiat Neurol Scand*, 112(suppl), pp. 1–162.

Mace, C. J. and Trimble, M. R. (1996) 'Ten-year prognosis of conversion disorder.', *British Journal of Psychiatry*, 169, pp. 282–8.

McKenzie, P. *et al.* (2010) 'Early outcomes and predictors in 260 patients with psychogenic nonepileptic attacks', *Neurology*, 74, pp. 64–69. doi: 10.1212/WNL.0b013e3181c7da6a.

McKenzie, P. S. *et al.* (2011) 'Do patients whose psychogenic non-epileptic seizures resolve, "replace" them with other medically unexplained symptoms? Medically unexplained symptoms arising after a diagnosis of psychogenic non-epileptic seizures.', *Journal of neurology, neurosurgery, and psychiatry*, 82, pp. 967–969. doi: 10.1136/jnnp.2010.231886.

McKeon, A. *et al.* (2009) 'Psychogenic tremor: long-term prognosis in patients with electrophysiologically confirmed disease.', *Movement disorders : official journal of the Movement Disorder Society*, 24(1), pp. 72–76. doi: 10.1002/mds.22301.

Meierkord, H. *et al.* (1991) 'The clinical features and prognosis of pseudoseizures diagnosed using video-EEG telemetry', *Neurology*, 41, pp. 1643– 1646.

Munhoz, R. P. *et al.* (2011) 'Cross-cultural influences on psychogenic movement disorders - a comparative review with a Brazilian series of 83 cases.', *Clinical neurology and neurosurgery*. Elsevier B.V., 113(2), pp. 115–8. doi: 10.1016/j.clineuro.2010.10.004.

O'Sullivan, S. S. *et al.* (2007) 'Clinical characteristics and outcome of patients diagnosed with psychogenic nonepileptic seizures: a 5-year review.', *Epilepsy & behavior : E&B*, 11, pp. 77–84. doi: 10.1016/j.yebeh.2007.04.003.

Oishi, N. *et al.* (2009) 'Acute-onset unilateral psychogenic hearing loss in adults: Report of six cases and diagnostic pitfalls', *Orl*, 71, pp. 279–283. doi: 10.1159/000251195.

Pehlivantürk, B. and Unal, F. (2002) 'Conversion disorder in children and adolescents: A 4-year follow-up study', *Journal of Psychosomatic Research*, 52, pp. 187–191. doi: 10.1016/S0022-3999(01)00306-3.

Ramani, V., Girgenti, L. and Hickling, E. (1996) 'Outcome after diagnosis of psychogenic nonepileptic seizures (PNES)', *Epilepsia*, 37, pp. 416–417.

Reilly, C. *et al.* (2013) 'Psychogenic nonepileptic seizures in children: A review', *Epilepsia*, 54(10), pp. 1715–1724. doi: 10.1111/epi.12336.

Reuber, M. *et al.* (2003) 'Outcome in psychogenic nonepileptic seizures: 1 to 10-year follow-up in 164 patients', *Annals of Neurology*, 53, pp. 305–311. doi: 10.1002/ana.3000.

Reuber, M. *et al.* (2005) 'Measuring outcome in psychogenic nonepileptic seizures: how relevant is seizure remission?', *Epilepsia*. Academic Neurology Unit, University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK. mreuber@doctors.org.uk, 46(11), pp. 1788–95. doi: 10.1111/j.1528-1167.2005.00280.x.

Riaz, H. *et al.* (1998) 'Non-epileptic pilot study attack disorder and clinical outcome : a', pp. 365–368.

Ricciardi, L. *et al.* (2015) 'Symptom severity in patients with functional motor symptoms: Patient's perception and doctor's clinical assessment', *Parkinsonism and Related Disorders*. Elsevier Ltd, 21(5), pp. 529–532. doi: 10.1016/j.parkreldis.2015.02.022.

Schrag, A. *et al.* (2004) 'The syndrome of fixed dystonia: An evaluation of 103 patients', *Brain*, 127(10), pp. 2360–2372. doi: 10.1093/brain/awh262.

Schwingenschuh, P. *et al.* (2008) 'Psychogenic movement disorders in children: a report of 15 cases and a review of the literature', *Mov Disord.* Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, London, United Kingdom, 23(1531-8257 (Electronic)), pp. 1882–1888.

Selwa, L. M. *et al.* (2000) 'Nonepileptic seizure outcome varies by type of spell and duration of illness.', *Epilepsia*, 41(10), pp. 1330–1334. doi: 10.1111/j.1528-1157.2000.tb04613.x.

Sharpe, M. *et al.* (2010) 'Neurology out-patients with symptoms unexplained by disease: illness beliefs and financial benefits predict 1-year outcome.', *Psychological medicine*, 40, pp. 689–698. doi: 10.1017/S0033291709990717.

Silva, W. *et al.* (2001) 'Clinical features and prognosis of nonepileptic seizures in a developing country', *Epilepsia*, 42(3), pp. 398–401. doi: 10.1046/j.1528-1157.2001.45299.x.

Slater, E. T. (1965) 'Diagnosis of 'hysteria'', *BMJ : British Medical Journal*, i, pp. 1395–1399.

Slater, E. T. and Glithero, E. (1965) 'A follow up study of patients diagnosed with hysteria.', *Journal of psychosomatic research*, 9, pp. 9–13.

Sletteberg, O., Bertelsen, T. and Høvding, G. (1989) 'The prognosis of patients with hysterical visual impairment.', *Acta ophthalmologica*, 67, pp. 159–163.

Stone, J. *et al.* (2003) 'The 12 year prognosis of unilateral functional weakness and sensory disturbance', *Journal of Neurology, Neurosurgery & Psychiatry*. Division of Clinical Neurosciences, School of Molecular and Clinical Medicine, University of Edinburgh, Edinburgh, UK. jstone@skull.dcn.ed.ac.uk: BMJ Publishing Group Ltd, 74(5), pp. 591–596. doi: 10.1136/jnnp.74.5.591.

Stone, J. (2005) 'Systematic review of misdiagnosis of conversion symptoms and "hysteria"', *BMJ*, 331(7523), pp. 989–0. doi: 10.1136/bmj.38628.466898.55.

Stone, J. *et al.* (2009) 'Symptoms "unexplained by organic disease" in 1144 new neurology out-patients: how often does the diagnosis change at follow-up?', *Brain*. Division of Clinical Neurosciences, School of Molecular and Clinical Medicine, University of Edinburgh, Western General Hospital, Edinburgh, UK. jon.stone@ed.ac.uk, 132(1460-2156 (Electronic)), pp. 2878–2888. doi: 10.1093/brain/awp220.

Stone, J. and Carson, A. (2011) 'Functional neurologic symptoms: assessment and management', *Neurologic clinics*. Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. Jon.Stone@ed.ac.uk: Elsevier, 29(1557-9875 (Electronic)), pp. 1–18. doi: 10.1016/j.ncl.2010.10.011.

Thomas, M., Dat Vuong, K. and Jankovic, J. (2006) 'Long-term prognosis of patients with psychogenic movement disorders', *Parkinsonism & Related Disorders*, 12(6), pp. 382–387. doi: 10.1016/j.parkreldis.2006.03.005.

Toldo, I. *et al.* (2010) 'Nonorganic (psychogenic) visual loss in children: a retrospective series.', *Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society*, 30, pp. 26–30. doi: 10.1097/WNO.0b013e3181c252b9.

Toth, C. (2003) 'Hemisensory syndrome is associated with a low diagnostic yield and a nearly uniform benign prognosis', *Journal of Neurology Neurosurgery and Psychiatry*, 74(8), pp. 1113–1116. doi: 10.1136/jnnp.74.8.1113.

Walczak, T. S. *et al.* (1995) 'Outcome after diagnosis of psychogenic nonepileptic seizures', *Epilepsia*, 36, pp. 1131–1137. doi: 10.1111/j.1528-1157.1995.tb00472.x.

Wig, N. and Mangalwedhe, K. (1982) 'A follow up study of Hysteria', *Indian Journal of ...*, (24), pp. 120–125.

Williams, D. T., Ford, B. and Fahn, S. (1995) 'Phenomenology and psychopathology related to psychogenic movement disorders.', *Advances in neurology*, 65, pp. 231–257.

Chapter 8.

The prognosis of functional limb weakness, a 14-year case-control study.

Gelauff JM, Carson A, Ludwig L, Tijssen MAJ, Stone J.

Article published in Brain 2019, doi: 10.1093/brain/awz138.

8. What is the prognosis of functional weakness? A 14-year follow-up study.

1. How often does the diagnosis change?

METHODS
consensus meeting using information from records, patients and their GPs

RESULTS

	functional limb weakness (n=89)	neurological controls (n=41)
misdiagnosis	1 (1%)	1 (2%)
de novo disease	3 (4%)	1 (2%)
diagnostic refinement	–	2 (5%)
prodomal change	3 (4%)	–

In both groups the diagnosis was wrong in 1 patient: 1 patient in the functional weakness group had MS, 1 patient in the neurological control group MSA.

2. How many patients died and of what cause?

METHODS
National Registry Death Certificates

primary cause in the functional weakness group:
cardiovascular disease
infectious diseases
malignancy

RESULTS

patients per group: 99
functional limb weakness
11 died

patients per group: 45
neurological controls
8 died

1 died

patients per group: 30
healthy control

11 patients with functional limb weakness, 8 neurological controls and 1 healthy control had died.

3. Did the functional limb weakness improve after 14 years?

RESULTS

remitted

much improved

improved

same

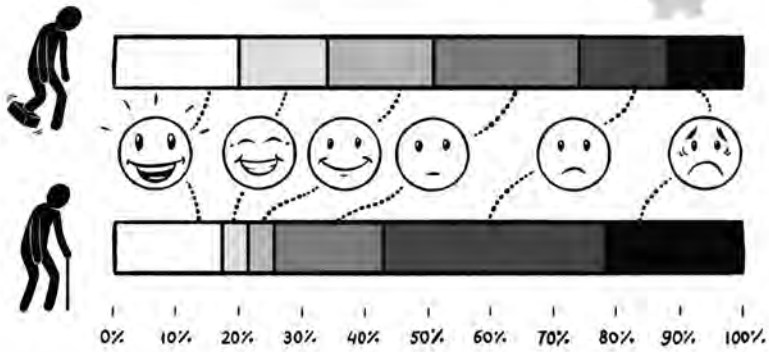
worse

much worse

METHODS
questionnaire

functional limb weakness (n=65)

neuro-logical controls (n=23)



4. Can we predict outcome?

METHODS
predictor analysis (baseline → follow-up)

RESULTS

BASELINE VARIABLES → FUNCTIONAL LIMB WEAKNESS

baseline

follow-up

2000-2003

2015-2016

baseline factors with negative influence on outcome: univariate only

somatization disorder

pain

high total symptom count

poor general health

ABSTRACT

Reliable data on the prognosis of functional motor disorder are scarce, as existing studies of the prognosis of functional motor disorder are nearly all retrospective, small and uncontrolled. In this study we used a prospectively recruited, controlled cohort design to assess misdiagnosis, mortality and symptomatic and health outcome in patients with functional limb weakness compared to neurological disease and healthy controls. We also performed an exploratory analysis for baseline factors predicting outcome.

107 patients with functional limb weakness, 46 neurological and 38 healthy controls from our previously studied prospective cohort were traced for follow-up after an average of 14 years. Misdiagnosis was determined in a consensus meeting using information from records, patients and their GPs. Numbers and causes of death were collected via death certificates. Outcome of limb weakness, physical and psychiatric symptoms, disability/quality of life and illness perception were recorded with self-rated questionnaires. Outcome measures were compared within and between groups.

Seventy-six patients (71%) with functional limb weakness, 31 (67%) neurological and 23 (61%) healthy controls were included in follow-up. Misdiagnosis was found in one patient in the functional limb weakness group (1%) and in one neurological control (2%). Eleven patients with functional limb weakness, 8 neurological controls and 1 healthy control had died. Weakness had completely remitted in 20% of patients in the functional limb weakness group and in 18% of the neurological controls (p=0.785) and improved in a larger proportion of functional limb weakness patients (p=0.011). Patient outcome was comparable between patient groups, but worse than outcomes in healthy controls. No baseline factors were independent predictors of outcome, although somatisation disorder, general health, pain and total symptoms at baseline were univariably correlated to outcome.

This study is the largest and longest follow-up study of functional limb weakness. Misdiagnosis in functional limb weakness is rare after long-term follow-up. The disorder is associated with a higher mortality rate than expected, and symptoms are persistent and disabling. It appears difficult to predict outcome based on common baseline variables. These data should help inform clinicians to provide a more realistic outlook of the outcome and emphasises the importance of active and targeted therapy.

INTRODUCTION

The prognosis of functional motor symptoms is unclear. Whilst there is growing recognition that the diagnosis is normally stable, there is a notable absence of data to guide clinicians in answering the key question patients ask- "will it get better?"

There is now scientific consensus, supported by systematic review, that poorly conducted but widely cited early reports of high rates of misdiagnosis were erroneous. Rates of diagnostic revision have been around 4% since 1970 [1]. But despite this, fears of misdiagnosis are still widely expressed, and some senior clinicians still extol the view that the diagnosis of functional symptoms should not be made for fear of clinical error. Our own large epidemiological study of patients presenting to neurologists with symptoms lacking a pathophysiological explanation, a wider phenotype than functional motor symptoms [2], found a much lower frequency of that diagnostic revision and highlighted that actual diagnostic error was rare (4 out of 1040) [3]. However, follow-up was only 18 months and it could be argued that many alternate diagnoses may only become apparent after the passage of time.

The Scottish Neurological Symptoms Study also had an intriguing secondary finding that a subgroup of patients with dissociative seizures had an unexpectedly high mortality rate of 5% (4 out of 80). This was partially replicated by Duncan et al [4] who found the premature (<75 years of age) death rate in dissociative seizures was somewhat higher compared to the local national death rate (0.58% compared to 0.41% per year). In functional motor symptoms the limited available data does not provide a meaningful answer [5–8].

Significantly, more attention has been paid to diagnostic accuracy than patients' actual outcomes. We conducted a systematic review of the prognosis of functional motor symptoms consisting of 24 studies with a duration of follow-up between 1.5 and 12.5 years, with only two longer than 10 years. We found that 39% were the same or worse at follow-up. However, most studies were small, retrospective, performed in tertiary centres, and without a control group. Studies were too heterogeneous for clear predictors to emerge but a long duration between the diagnosis and symptom onset were consistently associated with bad outcome [9].

In this study we describe the long term follow-up of a prospectively ascertained case-control cohort study of 107 patients with functional limb weakness [10,11]. We aimed: (1) to determine the rate and type of misdiagnosis in the functional limb

weakness group and the neurological control group; (2) to describe the frequency and cause of death in patients with functional limb weakness and compare it to neurological disease and healthy control groups from the same baseline study; (3) to determine the outcome of limb weakness in terms of change in the presenting symptom, physical and psychiatric symptoms, disability / quality of life and illness perceptions in patients with functional limb weakness compared to neurological controls (4) to conduct an exploratory analysis of baseline factors that predict poor outcome at follow-up in the functional limb weakness group.

METHODS

This study received ethical approval from the South Central – Oxford C research ethics committee, a body representing the UK Health Departments' Research Ethics Service (Rec reference: 14/SC/0209). Consent was obtained according to the declaration of Helsinki.

Baseline

Between 2000 and 2003, 107 patients with functional limb weakness, 46 patients with neurological disorders causing limb weakness (the neurological controls) and 38 healthy subjects (the healthy controls), were included. Patients with functional and neurological limb weakness were recruited consecutively by referral from all consultant neurologists working in South East Scotland (population about one million). Inclusion criteria for patients were: weakness/paralysis of one or more limb(s) diagnosed by a consultant neurologist as completely unexplained by organic disease for the functional weakness group, and completely explained by neurological disease in the neurological control group. Symptom onset had to be within the previous 2 years. Patients had to be over 16, able to consent and should not have an intellectual disability. Healthy control subjects, without neurological disease or limb weakness, were asked to take part when they visited their GP for a cervical smear, an oral anti-conceptive health check or a minor upper respiratory tract infection. Four studies have been published on the baseline data [10–13].

Follow-up

We located participants from the original study using the electronic record system of NHS Lothian (TRAK) and by contacting GPs (in some cases via Practitioners Services Scotland). Subjects who agreed to participate provided written informed consent and were then asked to fill out a questionnaire, either online or on paper.

Misdiagnosis

The possibility of misdiagnosis was assessed from three overlapping sources: Patients were asked if 'a new diagnosis which explains the weakness at the time of the baseline study' had occurred during follow-up. The patients' GPs were asked the same question by means of a short postal questionnaire. Third, the electronic records system of NHS Lothian was searched to find any indication of misdiagnosis during the follow-up period. Records were classed as 'reviewed' if at least one medical record was available from 2012 onwards.

A consensus meeting (JS, AC and JG) was held to review this data and determine whether the initial symptoms of functional or neurological limb weakness could, with the benefit of hindsight, be explained better by another diagnosis. Not all diagnostic revision represents a 'misdiagnosis' and we categorised patients according to the classification of Stone *et al*. [3].

Deaths

We contacted the National Records of Scotland and England to determine if participants had deceased during the follow-up period. The primary and secondary cause of death was extracted from death certificates The UK uses WHO criteria in which the primary cause of death is the disease or event that started the chain of events that led to death, the secondary cause is either a consequence or complication of the primary cause, or another disease which might have contributed. These were then evaluated against the clinical data from the initial presentation.

OUTCOME

Outcome in patients and controls was measured by questionnaires. Change in severity of limb weakness in both patient groups was rated on a 6-point Likert scale ranging from 'completely remitted, to 'much worse'. Rates of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS). Overall symptom burden was measured using the current physical symptoms list on the adapted Illness Perceptions Questionnaire (IPQ). Disability/ quality of life was assessed using Medical Outcome Study Short form 36 items (SF36) and the Work and Social Adjustment Scale (WSAS) and questions on whether or not the subject was in work or studying, receiving social and/or health related benefits. Illness perceptions in patients were measured using selected items from the Illness Perception Questionnaire (IPQ) ('My illness is likely to be permanent rather than

temporary', 'My illness is a mystery to me', 'stress or worry was a cause for your weakness', 'damage to the nervous system was a cause for your weakness') scored on a 5-point Likert scale. Patients were asked if they received any treatment, and if so, if this was physiotherapy, psychotherapy and/or any other treatment during the follow-up period. Treatment was not explored further, because patient's recall of details of treatment was considered biased and unreliable after 12-16 years of follow-up.

Prognostic factors

Several baseline variables were selected for a prognostic factor analysis to predict change in severity of limb weakness (as measured by the CGI), and for the post-hoc comparison of patients in follow-up, not in follow-up and deceased, in order to find potential selection bias and predictors of death.

The selection of prognostic baseline variables (see results, table 4) was based on our systematic review on the prognosis of functional motor disorders [9], complemented with variables that predicted functional vs neurological limb weakness at baseline [10]. Prognostic factors were only assessed in the functional weakness group.

Most of these factors were based on standardised questionnaires (as described in Stone et al. 2010), these are listed in the corresponding tables. Deprivation category was determined based on postcode data (which is a measure of socioeconomic deprivation), registration of appendectomies and hysterectomies was part of the baseline inventory, as a marker of vulnerability to functional disorders. Change in severity of limb weakness, as measured by the CGI was used as the outcome measure. The selection of prognostic baseline variables (see results, table 4) was based on our systematic review on the prognosis of functional motor disorders [9], complemented with variables that predicted functional vs neurological limb weakness at baseline [10]. Prognostic factors were only assessed in the functional weakness group.

Statistical analysis

All patients were analysed in their initial group, irrespective of possible misdiagnosis. Misdiagnosis was reported as a percentage in both patient groups. The standardised mortality ratio (expected deaths based on national reports / measured deaths) was calculated for both patient groups. The number of people that died in Scotland from 2000 to 2015 was extracted from the National Records of Scotland. As patients were included in our study from 2000 untill 2003, standardised mortality ratios

for the cohorts from 2000, 2001 and 2002 up and until 2015 were compared to the corresponding cohorts in Scotland separately and a weighted mean standardised mortality ratio was calculated. Baseline characteristics of subjects in follow-up, not in follow-up and the deceased were compared between the three groups using non-parametric testing, in order to find potential selection bias and predictors of death (Chi Square, Kruskall-Wallis and Mann-Witney U testing). Baseline factors that were found to have a prognostic value, were selected post hoc for this comparison. No prognostic analyses were performed in patients who had deceased.

Patient outcomes were compared between (follow-up) and within group (follow-up versus baseline). Group comparisons with normally distributed continuous data were tested with T-tests (normal or paired for repeated measures). Continuous and categorical data that was not normally distributed was tested using non-parametric methods: Mann-Witney U or Chi square tests (between group analysis), Wilcoxon Signed Rank tests (within group analysis).

Prognostic factors were determined in the functional weakness group using binary logistic regression analysis. Weakness severity, the dependent variable, was dichotomised into same/ worse (bad) or better/remitted (good). Univariate testing was performed for all baseline factors, all factors that reached a p-value of $p<0.05$ were subsequently included in a multivariate analysis. The multivariate binary logistic regression was performed using backwards elimination.

Additionally, correlations using the non-parametric Spearman's Rho, were made between outcomes and the change from baseline to outcome, to determine if bad outcome of limb weakness is correlated to bad outcome in other domains. Also, correlations were made between improvement of secondary outcome measures and weakness outcome, to determine factors that might be interesting for targeting treatment.

All missing data was reported, no imputation methods were used. To correct for multiple comparisons, we handled interpretation of p-values cautiously and considered p values larger than 0.01 to be insignificant.

RESULTS

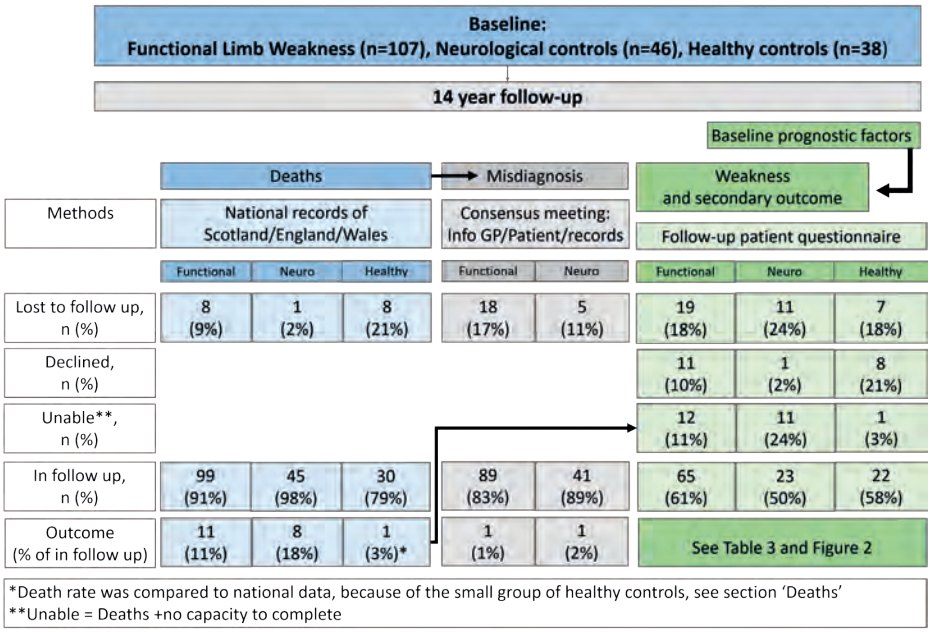


Figure 1. Flowchart follow-up. Misdiagnosis and patient outcome (including deaths) were studied parallel in the baseline population. Functional = Functional limb weakness, Neuro = neurological control subjects, Healthy = Healthy control subjects. *In 8 functional limb weakness patients, 1 neurological control and 8 healthy controls we did not have sufficient information to determine if they had died during follow-up. In 3 out of 65 functional limb weakness patients, only main outcome (acquired by phone) was available.

The mean follow-up duration was 14 years for functional limb weakness patients and neurological controls, (range 12-16 and 13-15 years respectively) and 13 years for healthy controls (range 12-15 years). Figure 1 shows a flowchart of follow-up, including misdiagnosis, deaths and patient outcome. Neurological controls that took part in the follow-up study had the following baseline diagnoses: Multiple Sclerosis (n=12), Guillain-Barré (n=4), transverse myelitis (n=3), clinically isolated syndrome (n=1), ganglionopathy (n=1), ulnar neuropathy (n=1), myasthenia gravis (n=1). From those who were lost to follow-up 14 out of 19 functional limb weakness patients, 10 out of 11 neurological controls and 6 out of 7 healthy patients had either definitely or probably moved out of South East Scotland. When patients in follow-up and not in follow-up were compared at baseline (see supplementary table 1), patients in the functional weakness group who were not in follow-up had a higher percentage of somatisation disorder (42% vs 20%, p=0.02). In the neurological control group, patients in follow-up had a significantly worse general health, compared to the group not in follow-up. The healthy control group did not show any differences.

Misdiagnosis

Sufficient data was available to determine whether there had been a change in diagnosis in 85% of the baseline cohort, comprising 89 functional limb weakness patients and 41 neurological controls. The data came from electronic records alone (n=49), combination of the patient and/or the GP and/or electronic records (n=40) (Table 1).

In the functional limb weakness group, one patient had a diagnosis of multiple sclerosis (MS), which, with hindsight could have been diagnosed at baseline with the information available at that time. However, it should be noted that this patient still had functional neurological symptoms comorbid to MS symptoms at follow-up. In addition, six patients developed a neurological disorder during the follow-up period that could not explain the initial functional limb weakness. In three of those patients (Huntington's disease, Parkinson's disease and idiopathic cerebellar degeneration), the consensus view was that whilst the disorder would not have directly explained the symptom of functional limb weakness, the prodromal phase of the neurological condition *may* have contributed to the development of functional weakness. Prodromal phases of neurodegenerative diseases may promote functional disorders for many reasons, including altered somatosensory feeling in the limb, or because of alterations in cognition and emotions, especially in relation to attentional processing. In the three cases of ischaemic stroke there were strong reasons to argue the initial functional limb weakness was not related (onset, anatomical location or normal MRI at baseline) and was therefore not considered a TIA or stroke. Finally, for one patient there was uncertainty, at follow-up, whether this patient had a combination of a functional disorder and MS with very limited symptomatology, or only a functional disorder.

In the neurological control group one patient was categorised as misdiagnosis. The diagnosis of common peroneal palsy was with the benefit of hindsight an early sign of Spinal Muscle Atrophy (the stated cause of death in this patient) and therefore labelled as misdiagnosis. One patient developed functional symptoms during follow-up on top of the neurological diagnosis and is therefore categorised as 'de novo development of 'functional disorder'. Two neurological controls with a single episode of demyelination at baseline, developed more episodes, therefore the diagnosis changed to MS. Table 1 summarises these findings.

Functional limb weakness patients (n=89)			Neurological controls (n=41)	
Change of diagnosis category*	**N**	**Follow-up Diagnosis**	**N**	**Follow-up Diagnosis**
Misdiagnosis	1	Multiple Sclerosis and Functional Disorder	1	Common peroneal nerve palsy changed to Spinal Muscle Atrophy
Diagnostic refinement	-	-	2	Clinically Isolated Syndrome evolving to MS
De novo development of new disease/disorder	3	3x ischaemic stroke	1	New functional disorder in MS patient
Possible prodromal diagnostic change	3	Huntington's disease, Parkinson's disease, Idiopathic cerebellar degeneration		
Disagreement between doctors	1	Disagreement between "MS and functional disorder" vs only functional disorder		

Table 1. Change in diagnosis during follow-up. * from Stone et al. [3].

Deaths

In 101 functional limb weakness patients (94%), 45 neurological controls (94%) and 30 healthy controls (79%) we had sufficient information to determine if they had died during follow-up. Eleven functional limb weakness patients, eight neurological controls and one healthy control had died.

The cause of death is shown in table 2. Within the functional group, the deceased were older at symptom onset, had a worse general health and were in a lower deprivation category at baseline, compared to all other functional limb weakness patients. No such differences were found within the neurological control group. There was no difference in the number of smokers or opioid users between the deceased group and the other patients at baseline, (supplementary table 1), although the absolute values of the numbers of smokers were 25% in follow-up compared to 45% in the deceased group, raising the possibility of a type 2 error due to small numbers.

The primary cause of death in the functional limb weakness group were all non-neurological. In three cases the secondary cause of death was a neurological disorder that patients developed after their initial episode of functional weakness; these cases (two with an ischaemic stroke unrelated to initial presentation and one suffering from idiopathic cerebellar degeneration) were discussed above. For two patients no death certificates were available in the UK and we were unable to trace location of death outside of the UK.

In the neurological control group 6 out of 8 patients' deaths were related to their initial known diagnoses, either as a primary or secondary cause of death (glioblastoma (n=2), multiple sclerosis (n=2), motor neuron disease /spinal muscular atrophy (n=2)).

The (weighted mean) standardised mortality ratio for the death rate under 75 years of age for the functional weakness group was 1.48 and 2.4 for the neurological control group.

	Functional limb weakness (n=101)		**Neurological controls (n=45)**		**Healthy controls (HC) (n=30)**	**Functional vs neuro**
Deaths	11 (11%)		8 (18%)		1 (3%)	P = 0.54
Mean age at onset of symptoms (years)	47 (SD 15)		41 (SD 12)		NA	P = 0.310
Mean age at death (years)	56 (SD 14.2)		48 (SD 13.6)		59	P = 0.079
Cause of death	**Primary**	**Secondary**	**Primary**	**Secondary**	**Primary**	
Cardiovascular	5	2		1	NA	-
Malignancy (non-neurological)	1				1	-
Infectious disease	2	1	3	1		
Neurological disorder		3	4	2	NA	-
Other	1*		1		NA	-
Unknown	2		-		-	
Death related to initial presentation with limb weakness	None		6 (75%)		NA	-
Standardised mortality ratio (weighted mean)	1.48		2.4		-	

Table 2. Deceased subjects. Based on data of 176 out of 191 baseline subjects (92%). Comparison of age: Mann Whitney U test, comparison of number of deaths: Chi square test. Causes of death (both primary as secondary) are given as stated on the death certificate. Secondary neurological disorders in the functional group were idiopathic cerebellar degeneration and ischaemic stroke(2). *Cause of death: Systemic sclerosis.

PATIENT OUTCOMES

Table 3 shows all outcome measures at baseline and follow-up for the three groups.

Functional limb weakness symptom outcome

Functional limb weakness completely remitted in 20%, improved in 31% (14% much improved, 17% improved) and remained the same or worsened in 49% (23% same, 14 % worse, 12 % much worse) of patients. In the neurological control group, limb weakness completely remitted in 18%, improved in 8% (4% much improved, 4 % improved) and remained the same or worsened in 74% (17% same, 35% worse, 22% much worse). A significantly larger percentage of patients improved in the functional limb weakness group (p = 0.011 on the Mann-Whitney U test across all categories) but complete remission was equally low in both groups (p=0.785) (Fig 2).

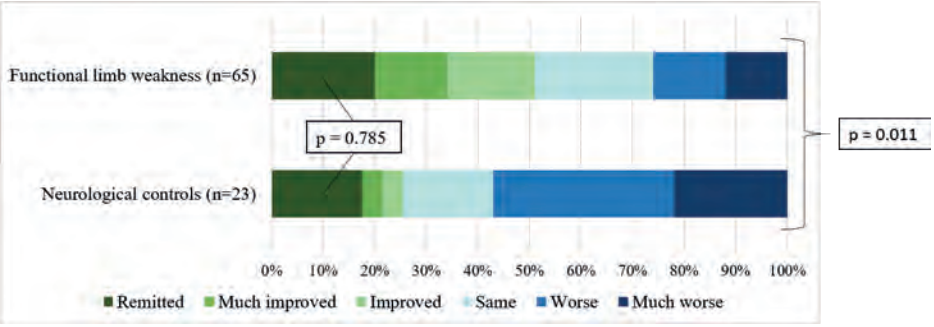


Figure 2. The severity of limb weakness at follow-up in the functional limb weakness group and the neurological control group. A Mann-Whitney U test comparing the whole scale in both groups, provided a p-value of 0.011.

Depression and Anxiety

Depression scores on the HADS were slightly better at follow-up than baseline in the functional limb weakness group, but this did not reach significance (52% at baseline versus 37% at follow-up, above the cut-off of 8, p=0,137). In the neurological control group, percentage of patients above the cut-off of 8, decreased from 41% to 27% (p=0.508), with no statistical difference. In the healthy controls, numbers changed from 32% to 11% (p=0.219). Follow-up depression scores in the functional limb weakness group were not statistically different from the neurological control group (p=0.616) and scores were worse than the healthy control group (p=0.037).

Mean anxiety levels on the HADS were comparable in the three groups at follow-up, using a cut off score of 8 or above, 69% of functional weakness patients, 36% of neurological controls and 42% of healthy controls suffered from anxiety, which was not statistically different.

Global symptom burden

Compared to baseline, we did not find a change in the number of co-morbid symptoms, measured on the IPQ symptom list, in patients with a functional disorder (baseline median 9, IQR4, follow-up median 8, IQR5, p=0.076) or neurological controls (baseline median 8, IQR3, follow-up median 7, IQR5, p=0.986), nor a difference between patient groups at follow-up (p=0.292). In healthy controls, only data at follow-up was available (median 3, IQR4). They scored significantly lower than the functional limb weakness group (p<0.001).

Disability / Quality of Life

At follow-up, 54% of the functional limb weakness patients reported fair or poor general health compared to 39% in the neurological control group (p=0.122) and 9% in the healthy control group (p<0.001). In none of the groups there was a significant change compared to baseline. Functional limb weakness patients and neurological controls scored similarly on all subdomains of the health-related quality of life and functioning SF-36 scale at follow-up, except for pain, which was worse in the functional limb weakness group (p=0.018). The functional limb weakness group scored significantly worse on almost all of these domains (physical functioning, physical role functioning, energy, pain) compared to the healthy control group, except for the emotional-role functioning domain and the social functioning domain.

At follow-up in the functional limb weakness group, 41% were not employed for health related reasons. In comparison, 39% versus 9% respectively were out of work for health-related reasons in the neurological and healthy control groups. The work and social adjustment scale showed similar outcomes in functional and neurological groups, while healthy controls were much less impaired. As at baseline, there was no statistical difference in the number of patients in receipt of state related financial benefits at follow-up between functional and neurological groups (43% vs 65%, p=0.066).

Illness perception

At baseline, 89% of patients with functional limb weakness agreed or strongly agreed that the limb weakness they experienced was a mystery to them, while at follow-up this was 51% (p<0.001). At baseline, 23% of patients agreed *stress or worry* was a causative factor for their limb weakness , versus 19% at follow-up (p=0.695) and for *damage to the nervous system* the percentages were 31% at baseline and 32% at follow-up (p=0.186), suggesting remarkable stability of illness beliefs.

	Functional weakness (n in follow-up = 63)			Neurological controls (n in follow-up = 23)			Healthy controls (n in follow-up = 22)			Functional weakness vs neuro controls follow-up	Functional weakness vs healthy controls follow-up
	Baseline	Follow-up	Baseline vs follow-up	Baseline	Follow-up	Baseline vs follow-up	Baseline	Follow-up	Baseline vs follow-up		
Depression and Anxiety (HADS), % at or above cut off score of 8											
Depression	52%	37%	p=0.137[4]	41%	27%	p=0.508[4]	32%	11%	p=0.219[4]	p=0.616[2]	**p=0.037**[2]
Anxiety	47%	69%	p=0.383[4]	14%	36%	p=0.063[4]	11%	42%	**p=0.031**[4]	p=0.226[2]	p=0.322[2]
Physical symptoms (IPQ plus 5 neurological symptoms)											
Symptom list, median (IQR)	9 (4)	8 (5)	p=0.076[3]	8 (3)	7(5)	p=0.986[3]	NA	3 (4)	NA	p=0.292	p<0.001[3]
Health related quality of life and functioning (SF-36)*											
General health, % fair/poor [1]	42%	54%	p=0.176[3]	14%	39%	p =0.179[3]	11%	9%	p=0.589[3]	p=0.122[1]	**p<0.001**[1]
Physical functioning, median (IQR)	35 (49)	55 (70)	p = 0.126[3]	45 (65)	30 (75)	p=0.204[3]	95 (10)	90 (16,25)	p=0.113[3]	p=0.487[1]	**p<0.001**[1]
Role physical, median (IQR)	0 (19)	0 (100)	**p=0.006**[3]	13 (75)	25 (75)	p=0,778[3]	100 (0)	100 (100)	p=0.269[3]	p=0.912[1]	**p<0.000**[1]
Role emotional, median (IQR)	33 (100)	100 (100)	**p=0.039**[3]	100 (42)	100 (100)	p=0.434[3]	100 (0)	100 (100)	p=0.931[3]	p=0.777[1]	p=0.151[1]
Energy, median (IQR)	25 (40)	40 (40)	**p=0.036**[3]	33 (36)	33 (53)	p=0.444[3]	50 (15)	70 (27)	**p=0.002**[3]	p=0.930[1]	**p<0.001**[1]
Pain, median (IQR)	33 (35)	20 (20)	**p<0.001**[3]	50 (24)	20 (20)	**p<0.001**[3]	50 (40)	40 (20)	**p=0.007**[3]	**p=0.018**[1]	**p<0.001**[1]
Social functioning, median (IQR)	44 (38)	50 (25)	p=0.535[3]	50 (53)	50 (12,5)	p=0.547[3]	50 (25)	50 (12,5)	**p=0.015**[3]	p=0.193v	p=0.157[1]
Work, social adjustment and benefits											
WSAS score, median (IQR)	NA	17 (27)	NA	NA	18 (19)	NA	NA	0 (8,75)	NA	p=0.868[1]	**p<0.001**[1]
In paid employment	34%	40%	**p<0,001**[3]	70%	39%	p=0.015[3]	95%	68%	p=0.012[3]	p=0.960[2]	**p=0.018**[2]
Unemployed health related	62%	41%		22%	39%		0%	9%			
Any benefits	49%	43%	p=0.332[4]	30%	65%	p=0.021[4]	4,5%	9%	p=1.00[4]	p=0.066[2]	p=0.004[2]

Table 3. Outcome measures in patients and controls. SF36 functioning and disability scale (range 0-100): high score means better functioning or less pain). Work and social adjustment scale, (range 0-40): higher score means worse impairment). *Data on the SF36 general health question was available in 65 functional patients (instead of 63). Missing data: SF36 and HADS baseline data in 1 functional weakness patient, 1 neurological control and 3 healthy controls. Statistical analysis: [1]Mann-Whitney U test, [2]Chi square test, within group: [3]Wilcoxon signed rank or [4]McNemar (for binominal data).

Treatment

52% of functional limb weakness patients versus 70% of neurological controls (p = 0.154) reported receiving some form of treatment for their limb weakness during the follow-up period. Of the functional weakness patients, 76% reported receiving physiotherapy at some stage during the follow-up period, and 36% reported received psychotherapy. In the neurological control group, 75% reported physiotherapy, and only one patient reported psychotherapy. Other therapies in the neurological control group included medication for the underlying condition.

Prognostic factors and correlations

Univariate analysis of prognostic factors in the functional limb weakness group, is shown in Table 4. Patients with baseline presence of somatisation disorder (0.22 (0.05-0.89) p =0.034), pain (1.04 (1.01-1.06) p=0.007) and a high number of physical symptoms (0.84 (0.72-0.19=0) p=0.037) were less likely to improve. Patients with a better general health score on the SF36 at baseline (1.03 (1.00-1.05) p=0.017) were more likely to improve. The multivariate analysis showed none of the factors alone significantly predicted weakness outcome. This multivariate model provided a Cox and Snell R squared of 0.17, suggesting that these factors were only explaining a small amount of the variance.

In the functional weakness group, several follow-up outcome measures: general health, physical functioning, pain, energy, work and social adjustment and the total number of symptoms on the IPQ symptom list, showed significant correlations with weakness severity at follow-up, (supplementary table 2). Depression and anxiety did not correlate with weakness outcome. In the neurological group this was only the case for physical functioning. Change in energy correlated only weakly to a change in weakness severity in the functional group (rho -0.361 p=0.004). In the neurological group, a change in physical functioning correlated strongly to change in weakness severity (rho -0.712, p<.001), change in pain correlated moderately to a change in weakness severity (rho -0.610, p=0.003). Any treatment during the follow-up period did not influence weakness severity outcome in both groups.

	Limb Weakness Severity (CPS)			
	Univariate analysis		Multivariate analysis	
Baseline variables	**Odds ratio (CI 95%)**	**p-value**	**Odds ratio (CI 95%)**	**p-value**
Age at onset	1.01 (0.96-1.05)	0.829	-	-
Gender	1.25 (0.30-5.15)	0.757	-	-
Symptom duration	0.98 (0.92-1.04)	0.474	-	-
Being in work	1.13 (0.81-1.57)	0.486	-	-
Benefits	0.43 (0.16-1.18)	0.100	-	-
Deprivation category	0.64 (0.41-1.00)	0.050		
Appendectomy	0.70 (0.24-2.10)	0.528	-	-
Hysterectomy	0.30 (0.08-1.10)	0.069	-	-
Psychiatric co-morbidity and childhood trauma				
Depression (HADS)	0.99 (0.90-1.08)	0.769	-	-
Anxiety (HADS)	0.95 (0.86-1.04)	0.273	-	-
Somatisation Disorder (SCID)	0.22 (0.05-0.89)	0.034	0.44 (0.09-2.14)	0.312
Total psychiatric diagnoses on SCID	0.81 (0.58-1.13)	0.210	-	-
Physical abuse (CTQ)	1.00 (0.89-1.13)	1.000	-	-
Sexual abuse (CTQ)	1.02 (0.93-1.12)	0.723	-	-
Health related quality of life and functioning (SF36)				
General health	1.03 (1.00-1.05)	0.017	1.02 (1.00-1.04)	0.085
Physical functioning	1.02 (1.00-1.03)	0.065	-	-
Pain	1.04 (1.01-1.06)	0.007	1.03 (1.00-1.06)	0.030
Energy	1.01 (0.99-1.04)	0.268	-	-
Illness Perception (IPQ)				
'my weakness is a mystery to me'	1.08 (0.57-2.05)	0.808	-	-
'my weakness is permanent rather than temporary'	0.82 (0.55-1.22)	0.330	-	-
'what I do can determine if my illness gets better or worse'	1.23 (0.77-1.96)	0.392	-	-
'damage to nervous system caused my symptoms'	1.12 (0.70-1.80)	0.628	-	-
'stress or worry caused my symptoms'	1.14 (0.78-1.67)	0.487	-	-
'I wish the doctor had listened more'	0.83 (0.54-1.24)	0.353	-	-
'I have lost faith generally in doctors'	0.96 (0.67-1.36)	0.804	-	-
IPQ number of symptoms	0.84 (0.72-0.99)	0.037	0.93 (0.78-1.10)	0.375

Table 4. Prognostic factors. Univariate and multivariate binary logistic regression analysis of baseline factors on two dichotomised outcome measures. For both outcome measures, the relationship of baseline factors with good outcome is displayed. R squared (Cox and Snell) 0,17.

DISCUSSION

This study is the largest and longest prospectively recruited follow-up study of functional limb weakness, and it also includes a neurological and healthy control group. It is also the longest follow-up study ever for any functional neurological disorder [14].

Misdiagnosis

In this study, we found only one example of clear-cut misdiagnosis of functional limb weakness (1/89=1%), which was half the misdiagnosis rate of the neurological control group (1/41=2%). In three additional patients the development of functional limb weakness may have been part of a non-specific prodrome to the development of a neurodegenerative condition not associated with limb weakness. This in line with observations that functional neurological disorders often occur in the context of recognised neurological disease [15–17].

Even accounting for these possible prodromal cases, the misdiagnosis rate was low, and in keeping with other recent studies of functional neurological disorders, as discussed in the introduction. Our prospectively ascertained follow-up data was acquired over a much longer time period than any other study and provide important evidence of the stability and persistence of the symptoms in patients with functional limb weakness. These findings should encourage physicians to consider misdiagnosis in this patient population no more of an issue than in other neurological conditions . Reluctance to make a positive diagnoses of a functional motor disorder, or diagnostic uncertainty can powerfully impair treatment. We recommend that physicians should continue to reconsider any neurological diagnosis and remain vigilant of comorbid neurological disease, which is a powerful risk factor for all functional disorders. Our findings create an argument for neurologists to stay involved with the long term management of at least some patients with functional limb weakness, to guide treatment and detect neurological disease, sometimes occurring years after start of the functional symptoms.

Deaths

In our cohort, we found a standardised mortality ratio for the death rate under 75 years of age for the functional weakness group of 1.48 and of 2.4 for the neurological control group. Duncan et al. [18] found a death rate of 0,58% per year in a group of patients with psychogenic non-epileptic attacks (n=260). This was somewhat lower than our findings (our data converted to death rates: 0.77% per year in functional limb

weakness and 1.27% in neurological controls). In that study, as in ours, none of the causes of death were directly related to the initial symptoms. Cardiovascular cause of death was most frequent. There is very limited data on death rates from other follow-up studies in functional motor symptoms. From two studies in functional weakness, 1 patient out of 56 died after 12 years follow-up [5], and 5 out of 64 after 5-7 years of follow-up [6]. In the latter one patient died of pneumonia due to immobilisation (in a tetraplegic patient), one died of possible overdose, the others in these two studies died of cardiovascular disease or malignancy. These findings correspond generally to our findings. In two retrospective studies in movement disorders, 1 out of 25 [19] and 3 out of 88 [8] died, of whom one from suicide and the others of unrelated causes. The increased death rate in our cohort compared to the general population may have several causes: i) three patients died of neurodegenerative diseases, and their functional limb weakness may have been part of a prodromal state ; ii) secondary effects of having chronic illness including depression, anxiety or stress where present. iii) among patients with functional weakness patients, those that died had a poorer general health status at baseline compared to the patients that survived iv) it is possible that patients with functional weakness had a more sedentary lifestyle, because cause of death was often cardiovascular and a lower deprivation category was associated with death. However other cardiovascular factors were not found to be increased in the deceased group, although numbers were small, so caution is due for type two error.

Patient outcomes

In 80% of the functional limb weakness group, patients still had symptoms of weakness in one or more limb(s) after an average of 14 years follow-up, compared to 83% of patients in the neurological control group. There was a similar remission rate but overall better prognosis in the functional group compared to the neurological controls. The results are in line with our earlier retrospective follow-up study in which 83% of 42 patients still had weakness after 12,5 years [5]. Other smaller studies of outcome of patients with functional weakness, with 10 to 30 patients over 0.5-6 years, found a large range of outcomes with10 to 56% being the same or worse weakness at follow-up [20–23].

From a scientific perspective, it would be useful to investigate the natural history of untreated patients with functional limb weakness. Inevitably a large percentage of patients received some form of treatment (52% in the functional weakness group, 70% of neurological controls) during follow-up. Treatment did not correlate to outcome. However, the nature of these treatments remained unclear, as our study

was not focused on treatment, which were not standardised and randomised,. Also, we could not reliably collect data on types of treatment using self-report over a period of 14 years. One of the authors (JS) saw all the patients for research assessments at baseline between 2000 and 2003, not for specific treatment. Patients were told they were in a study of 'unexplained motor symptoms' only and didn't receive the detailed explanations, supported by written materials, that they would in 2019 in Edinburgh. The impression from review was that it was often not delivered by practitioners experienced in functional disorders.

Mirroring the persistent nature of the symptom of functional limb weakness, patients also failed to improve on most secondary health outcome measures. Total symptom burden and measures of disability/ quality of life were all correlated moderately to weakness severity, which (with the exception of physical functioning) were not found in the neurological control group. This could be due to quality of life being more greatly determined by functional symptoms in the functional weakness group compared to neurological controls.

More patients with functional limb weakness were out of work at follow-up than had been at baseline. Other studies of patients with functional motor disorders have found a low frequency of being in work ranging from 11% to 57% [20,24]. In our data, patients with functional weakness were less likely to receive benefits at follow-up (43%) than neurological controls (65%), although this did not reach significance (p=0.066), while disability at follow-up was equal. In contrast to findings from the Scottish Neurological Symptoms Study of 3781 outpatients [2], in which patients with functional disorders in general were slightly more likely to be on disability benefits, receipt of benefits did not predict outcome in patients with functional limb weakness.

Over time, financial benefits for functional limb weakness patients did not increase and receiving benefits did not predict outcome, which contradicts the notion that patients would perpetuate their symptoms in order to gain benefits.

Prognostic factors

Several factors were found to influence weakness severity at follow-up in the univariate analysis.

General health at baseline was, perhaps unsurprisingly, found to be associated with limb weakness outcome. Pain was also found to influence symptom outcome. From clinical practice we know pain is an important impairing symptom for many

functional limb weakness patients. However it has only been studied in fixed dystonia, where it found to be a negative predictor [25]. In our limb weakness study, many patients had worse pain scores at baseline (median score 33 out of 100, (IQR 35), lower score equates to more pain), and even worse (median 20, IQR 20, $p<0.001$) at follow-up, which was significantly worse again than the control groups. Also, a change in pain between baseline and follow-up was correlated to general health outcome. This highlights the importance of assessing pain at baseline and possibly targeting it as a stratifying factor in treatment trials.

Somatisation disorder at baseline, an indicator of individuals with functional symptoms in several domains, was also found to influence limb weakness at follow-up negatively in univariate analysis. In total 13 patients met the criteria for somatisation disorder at baseline, of those, 12 (92%) had poor or fair general health and 10 (77%) had same or worse weakness at follow-up. The two studies that have investigated this have found no correlation between somatoform disorders and outcome [24,25]. From our data, patients with a longstanding vulnerability to various symptoms throughout their life, do seem to have a worse prognosis. Total number of physical symptoms at baseline, which was found to be a univariate prognostic factor as well, could be seen in the same light.

The factors we included in the prognostic analysis were determined based on previous findings in the literature and in our baseline study, but many factors were not found to have a prognostic value. For age and gender, this was expected based on the literature. It was however striking that factors found to be predictive in other studies like benefits, working status, frequency of physical and sexual abuse and certain illness perceptions, were not prognostic [9]. Notwithstanding the risk of a false negative result, as our numbers are relatively low for a multivariate analysis, these are important observations, as many of these factors are often suggested to play an important role in the prognosis of functional neurological disorders.

Factors that have most consistently correlated with positive outcome in the literature included an early diagnosis and short duration of symptoms at baseline [8,21,24,26–33]. Symptom duration before diagnosis was not found to be a prognostic factor in our study. However, the original study set a maximum 2 years of symptom duration as an inclusion criterion at baseline which means this study could not easily look at that issue.

Generally, we found it difficult to predict outcome in our cohort, let alone at a patient level. Apart from the low yield of prognostic factors, part of the problem may be heterogeneity between patients. Moreover, our model only explained 17% of the variance of the functional weakness outcome, and 38% of the general health outcome, which means other unknown factors influence outcome substantially. In practice, this means that clinicians should be wary about judging the likely outcome in individuals with functional limb weakness and keep an open mind, regardless of apparently poor prognostic features.

LIMITATIONS

Inclusion to the original study was consecutively by all neurologists working in a regional clinical neurosciences centre covering the South east of Scotland region, population about one million. This is likely to be representative of the population in this region, as there is limited private medical care and in particular no inpatient private neurological beds. Incomplete ascertainment at follow-up is clearly a potential issue. However, our follow-up rate of 71% in the functional weakness group after 14 years (including the deceased patients) is respectable given the duration of time, and baseline variables appeared similar between responders and non-responders There was a higher percentage of patients with functional weakness in the group not in follow-up with somatisation disorder (42%) compared to the group in follow-up (20%). As we found somatisation disorder to be a (univariable) predictor of bad outcome, the higher drop-out of these patients could have caused bias towards more favourable outcome. Patients who could not be contacted had most commonly moved out of the area, so is arguably less likely to be a confounding factor. Patients declining to participate most likely introduced confounding, however whether that would be in favour of good or bad outcome is speculative. Our results on misdiagnosis may have been biased by the fact that these patients were all part of a study. Patients in whom there was doubt about the diagnosis may have been less likely to be referred to the study. Our data on cause of death is partly limited by accuracy of death certification. The patient outcome data was based on self-report. However, in previous studies comparing subjective and objective outcome measures there has been little difference between the two. Patients with very short duration of symptoms were not included in this study (ie if they had recovered by the time of the baseline assessment). As duration of symptoms has been found to be a negative prognostic factor [9], prognosis may be better in patients presenting to primary care or emergency settings.

CONCLUSION

Functional limb weakness can be diagnosed accurately and misdiagnosis is rare even after long term follow-up. Functional limb weakness is persistent, disabling, and associated with higher mortality than expected. It is very difficult to predict outcome based on common baseline variables, although pain and propensity to longstanding multiple functional disorders, may be important stratifying variables for clinical trials and treatment decision-making. These data should help clinicians to provide a more realistic prognosis for functional weakness patients and also stress the importance of active and targeted treatment.

Acknowledgements

We want to thank Rosemary Anderson for her help with obtaining death certificates. Also we want to thank Will Whiteley and Natasha Maurits for their assistance with the statistics of this manuscript.

Funding

JG was supported by a unrestricted research grant by the GSMS graduate school of the University of Groningen in order to perform her PhD. Furthermore she received travel grants from the COST dystonia EU action to visit Edinburgh. JS is supported by an National Research Scotland Career Fellowship. LL was supported by a DAAD scholarship (German Academic Exchange Service).

Competing interests

The authors report no competing interests.

SUPPLEMENTARY MATERIAL

Baseline data	Functional limb weakness				Neurological control subjects				Healthy control subjects		
	FU n= 65	NFU n=31	Deceased n=11	Tests	FU n = 23	NFU n=15	Deceased n = 8	Tests	FU n=22	NFU n=15	Tests
Age at symptom onset in years, mean(SD)	**38 (10)**	**35 (11)**	**48 (15)**	p=0.008[1]	39 (12)	34 (9)	42 (12)	NS	41 (10)	37 (16)	NS
Female (%)	86%	68%	73%	NS	87%	80%	75%	NS	95%	87%	NS
Deprivation category	**4 (1)**	**4 (1)**	**2 (1)**	p<0.001[4]	3 (1)	4 (2)	3 (3)	NS	3 (2)	4 (2)	NS
Hysterectomy (%)	22%	35%	0%	NS	4%	7%	13%	NS	4,5%	0%	NS
Benefits (%)	57%	68%	36%	NS	30%	53%	38%	NS	0%	0%	NS
Smoker (%)	**25%**	**48%**	45%	p=0.048[3]	39%	40%	63%	NS	13%	23%	NS
Opioid drugs user (%)	35%	29%	22%	NS	4%	13%	13%	NS	0%	0%	NS
Health related quality of life and functioning (SF36)											
General health (% fair/poor)*	**39%**	61%	**78%**	p=0.031[2]	**14%**	**69%**	25%	p=0.003[3]	10%	0%	NS
Physical functioning *	35 (49)	20 (35)	50 (55)	NS	45 (65)	25 (50)	23 (68)	NS	95 (10)	100 (5)	NS
Pain *	33 (35)	28 (33)	45 (19)	NS	50 (24)	45 (22)	38 (16)	NS	50 (40)	50 (25)	NS
Energy *	25 (40)	25 (20)	40 (45)	NS	33 (36)	45 (33)	35 (32)	NS	50 (25)	66 (40)	NS
Psychiatric co-morbidity											
Depression (HADS)*	8 (9)	7 (11)	11 (9)	NS	6 (8)	6 (8)	6 (11)	NS	4 (7)	4 (4)	NS
Anxiety (HADS)*	7 (9)	7 (10)	6 (7)	NS	4 (6)	4 (5)	8 (8)	NS	1 (4)	1 (2)	NS
Somatisation disorder (SCID) (%)	**20%**	**42%**	36%	p=0.024[3]	0%	0%	0%	NA	0%	0%	NA
Total psychiatric diagnoses (SCID)	2 (2)	2 (2)	3 (5)	NS	1 (2)	1 (2)	1 (1)	NS	0 (1)	0 (0)	NS
Illness perception (IPQ)											
'my illness is a mystery to me'	2 (1)	2 (2)	1 (1)	NS	4 (2)	2 (1)	2 (2)	NS	NA	NA	NA
'my symptoms are permanent rather than temporary'	3 (2)	3 (1)	3 (2)	NS	4 (2)	4 (1)	4 (2)	NS	NA	NA	NA

Supplementary table 1. Baseline comparison within and between group of participants in follow-up (FU), not in follow-up (NFU) and deceased subjects. Initial comparisons were made using chi square test and t-tests or Kruskall-Wallis test. In the healthy control group, the deceased are not included in the table, as in total only one patient died. * SF36 and HADS data was missing in 6 healthy control subjects, 6 cases and 3 neurological controls. One-by-one comparisons using Mann-Witney U test: [1]Deceased were significantly different from FU and NFU, [2]deceased were significantly different from FU, [3]FU is significantly different from NFU, [4]All groups differ from each other. Low deprivation category (range 1-7) corresponds to worse deprivation. SF36 functioning and disability scale (range 0-100): high score means better functioning or less pain). Work and social adjustment scale, (range 0-40): higher score means worse impairment).

	Functional weakness (n in follow-up = 63)		Neurological controls (n in follow-up = 23)	
Weakness severity at follow-up	**Spearman's rho**	**P-value**	**Spearman's rho**	**P-value**
Measures at follow-up:				
General health (SF36) at FU	0.55	p<0.001	0.41	0.053
Change in general health	-0.24	p=0.058	-0.26	p=0.244
Physical functioning (SF36) at FU	-0.58	p<0.001	-0.83	p<0.001
Change in physical functioning	-0.32	p=0.011	-0.71	**p<0.001**
Pain (SF36) at FU	-0.57	p<0.001	-0.40	p=0.062
Change in pain	-0.01	p=0.929	-0.61	**p=0.003**
Energy (SF36) at FU	-0.50	p<0.001	-0.41	p=0.050
Change in energy	-0.36	**p=0.004**	0.25	p=0.262
Work and social adjustment (WSAS) at FU	-0.47	p<0.001	0.59	p=0.003
Depression (HADS) at FU	0.32	p=0.009	0.36	p=0.096
Change in depression	0.25	p=0.051	-0.09	p=0.683
Anxiety (HADS) at FU	0.12	p=0.352	0.33	p=0.126
Change in anxiety	0.00	p=0.982	0.18	p=0.416
IPQ total symptoms	0.52	p<0.001	0.34	p=0.112
Change in response to 'my weakness is a mystery to me'	0.23	p=0.082	-0.03	p=0.898
Change in response to 'stress or worry caused my symptoms'	-0.13	p=0.304	0.09	p=0.702
Change in response to 'damage to nervous system caused my symptoms'	0.26	p=0.043	-0.02	p=0.944
Change in IPQ total symptoms	0.25	p=0.048	0.25	p=0.262
Any treatment	0.15	p=0.237	0.27	p=0.209

Supplementary table 2. Correlations at follow-up. Correlations between weakness outcome in the functional and neurological group and factors at follow-up (at FU) or differences between baseline and outcome (change).

REFERENCES

1. J. Stone, R. Smyth, A. Carson, S. Lewis, R. Prescott, C. Warlow, M. Sharpe, Systematic review of misdiagnosis of conversion symptoms and "hysteria"., BMJ. 331 (2005) 989. doi:10.1136/bmj.38628.466898.55.
2. A. Carson, J. Stone, C. Hibberd, G. Murray, R. Duncan, R. Coleman, C. Warlow, R. Roberts, A. Pelosi, J. Cavanagh, K. Matthews, R. Goldbeck, C. Hansen, M. Sharpe, Disability, distress and unemployment in neurology outpatients with symptoms "unexplained by organic disease," J. Neurol. Neurosurg. Psychiatry. 82 (2011) 810–813. doi:10.1136/jnnp.2010.220640.
3. J. Stone, a. Carson, R. Duncan, R. Coleman, R. Roberts, C. Warlow, C. Hibberd, G. Murray, R. Cull, A. Pelosi, J. Cavanagh, K. Matthews, R. Goldbeck, R. Smyth, J. Walker, a. D. Macmahon, M. Sharpe, Symptoms "unexplained by organic disease" in 1144 new neurology out-patients: how often does the diagnosis change at follow-up?, Brain. 132 (2009) 2878–2888. doi:10.1093/brain/awp220.
4. R. Duncan, M. Oto, J. Wainman-Lefley, Mortality in a cohort of patients with psychogenic non-epileptic seizures, J. Neurol. Neurosurg. Psychiatry. 83 (2012) 761–762. doi:10.1136/jnnp-2012-302900.
5. J. Stone, M. Sharpe, P.M. Rothwell, C.P. Warlow, The 12 year prognosis of unilateral functional weakness and sensory disturbance, J. Neurol. Neurosurg. Psychiatry. 74 (2003) 591–596. doi:10.1136/jnnp.74.5.591.
6. H.L. Crimlisk, K. Bhatia, H. Cope, A. David, C.D. Marsden, M.A. Ron, Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms, BMJ. 316 (1998) 582–586.
7. G. Deuschl, B. Koster, C.H. Lucking, C. Scheidt, Diagnostic and pathophysiological aspects of psychogenic tremors, Mov Disord. 13 (1998) 294–302.
8. A. Feinstein, V. Stergiopoulos, J. Fine, a E. Lang, Psychiatric outcome in patients with a psychogenic movement disorder: a prospective study., Neuropsychiatry. Neuropsychol. Behav. Neurol. 14 (2001) 169–176. doi:11513100.
9. J. Gelauff, J. Stone, M. Edwards, A. Carson, The prognosis of functional (psychogenic) motor symptoms: a systematic review., J. Neurol. Neurosurg. Psychiatry. 85 (2014) 220–6. http://www.ncbi.nlm.nih.gov/pubmed/24029543.
10. J. Stone, C. Warlow, M. Sharpe, The symptom of functional weakness: A controlled study of 107 patients, Brain. 133 (2010) 1537–1551. doi:10.1093/brain/awq068.
11. J. Stone, C. Warlow, M. Sharpe, Functional weakness: clues to mechanism from the nature of onset, J. Neurol. Neurosurg. Psychiatry. 83 (2012) 67–69. doi:10.1136/jnnp-2011-300125.
12. L. Ludwig, K. Whitehead, M. Sharpe, M. Reuber, J. Stone, Differences in illness perceptions between patients with non-epileptic seizures and functional limb weakness, J. Psychosom. Res. 79 (2015) 246–249. doi:10.1016/j.jpsychores.2015.05.010.
13. K. Whitehead, J. Stone, P. Norman, M. Sharpe, M. Reuber, Differences in relatives' and patients' illness perceptions in functional neurological symptom disorders compared with neurological diseases, Epilepsy Behav. 42 (2015) 159–164. doi:10.1016/j.yebeh.2014.10.031.
14. J. Gelauff, J. Stone, Prognosis of functional neurologic disorders, in: Handb. Clin. Neurol., 2016: pp. 523–541. doi:10.1016/B978-0-12-801772-2.00043-6.
15. J. Stone, A. Carson, R. Duncan, R. Roberts, R. Coleman, C. Warlow, G. Murray, A. Pelosi, J. Cavanagh, K. Matthews, R. Goldbeck, M. Sharpe, Which neurological diseases are most likely to be associated with "symptoms unexplained by organic disease," J. Neurol. 259 (2012) 33–38. doi:10.1007/s00415-011-6111-0.

16. I. Pareés, T.A. Saifee, M. Kojovic, P. Kassavetis, I. Rubio-Agusti, A. Sadnicka, K.P. Bhatia, M.J. Edwards, Functional (psychogenic) symptoms in Parkinson's disease, Mov. Disord. 28 (2013) 1622–1627. doi:10.1002/mds.25544.

17. B.D. Wissel, A.K. Dwivedi, A. Merola, D. Chin, C. Jacob, A.P. Duker, J.E. Vaughan, L. Lovera, K. LaFaver, A. Levy, A.E. Lang, F. Morgante, M.J. Nirenberg, C. Stephen, N. Sharma, A. Romagnolo, L. Lopiano, B. Balint, X.X. Yu, K.P. Bhatia, A.J. Espay, Functional neurological disorders in Parkinson disease, J. Neurol. Neurosurg. Psychiatry. (2018) jnnp-2017-317378. doi:10.1136/jnnp-2017-317378.

18. R. Duncan, C.D. Graham, M. Oto, Outcome at 5-10years in psychogenic nonepileptic seizures: What patients report vs. what family doctors report, Epilepsy Behav. 37 (2014) 71–74. doi:10.1016/j.yebeh.2014.06.011.

19. G. Deuschl, B. Köster, C.H. Lucking, C. Scheidt, Diagnostic and pathophysiological aspects of psychogenic tremors, Mov. Disord. 13 (1998) 294–302. doi:10.1002/mds.870130216.

20. M. Binzer, G. Kullgren, Motor conversion disorder. A prospective 2- to 5-year follow-up study., Psychosomatics. 39 (1998) 519–527. doi:10.1016/S0033-3182(98)71284-8.

21. E. Knutsson, a Mårtensson, Isokinetic measurements of muscle strength in hysterical paresis., Electroencephalogr. Clin. Neurophysiol. 61 (1985) 370–374. doi:10.1016/0013-4694(85)91027-2.

22. A. B. Carter, The prognosis of certain hysterical symptoms., Br. Med. J. 1 (1949) 1076–1079.

23. W. Brown, J. Pisetsky, Sociopsychologic factors in hysterical paraplegia., J Nerv Ment Dis. 119 (1954) 283–98.

24. H.L. Crimlisk, K. Bhatia, H. Cope, A. David, C.D. Marsden, M. a Ron, Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms, BMJ Br. Med. J. 316 (1998) 582–586.

25. N.M. Ibrahim, D. Martino, B.P.C. van de Warrenburg, N.P. Quinn, K.P. Bhatia, R.J. Brown, M. Trimble, a. Schrag, The prognosis of fixed dystonia: A follow-up study, Park. Relat. Disord. 15 (2009) 592–597. doi:10.1016/j.parkreldis.2009.02.010.

26. W. Couprie, E.F. Wijdicks, H.G. Rooijmans, J. van Gijn, Outcome in conversion disorder: a follow up study., J. Neurol. Neurosurg. Psychiatry. 58 (1995) 750–2.

27. J. Jankovic, K.D. Vuong, M. Thomas, Psychogenic Tremor : Long-Term Outcome, CNZ Spectr. 11 (2006) 501–8.

28. M. Thomas, K.D. Vuong, J. Jankovic, Long-term prognosis of patients with psychogenic movement disorders., Parkinsonism Relat. Disord. 12 (2006) 382–387. doi:10.1016/j.parkreldis.2006.03.005.

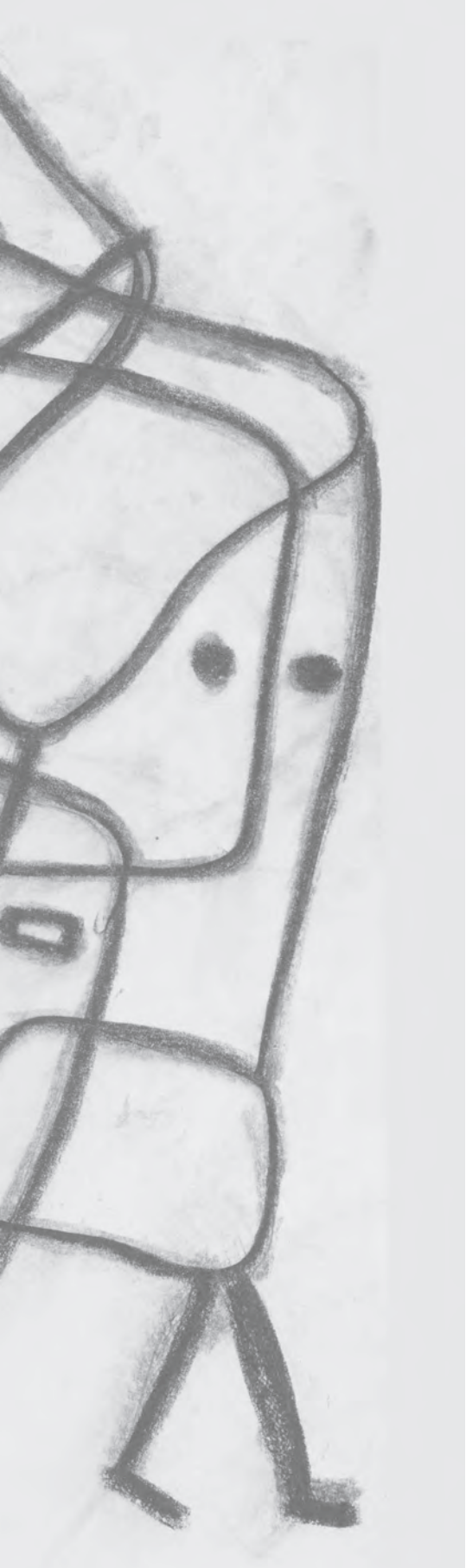
29. C.J. Mace, M.R. Trimble, Ten-year prognosis of conversion disorder., Br. J. Psychiatry. 169 (1996) 282–8.

30. R.P. Munhoz, J. a. Zavala, N. Becker, H. a G. Teive, Cross-cultural influences on psychogenic movement disorders - A comparative review with a Brazilian series of 83 cases, Clin. Neurol. Neurosurg. 113 (2011) 115–118. doi:10.1016/j.clineuro.2010.10.004.

31. S.A. Factor, G.D. Podskalny, E.S. Molho, Psychogenic movement disorders: frequency, clinical profile, and characteristics., J. Neurol. Neurosurg. Psychiatry. 95 (1995) 406–12.

32. R. Erro, M.J. Edwards, K.P. Bhatia, M. Esposito, S.F. Farmer, C. Cordivari, Psychogenic axial myoclonus: Clinical features and long-term outcome, Park. Relat. Disord. 20 (2014) 596–599. doi:10.1016/j.parkreldis.2014.02.026.

33. A. McKeon, J.E. Ahlskog, J.H. Bower, K. a Josephs, J.Y. Matsumoto, Psychogenic tremor: long-term prognosis in patients with electrophysiologically confirmed disease., Mov. Disord. 24 (2009) 72–76. doi:10.1002/mds.22301.



Part 3. Treatment

Chapter 9.

Treatment of Functional Motor Disorders

Gelauff JM, Dreissen YEM, Tijssen MAJ, Stone J.
*Both authors contributed equally to this work

Article published in Curr Treat Options Neurol 2014, doi: 10.1007/s11940-014-0286-5

OPINION STATEMENT

For the treatment of functional motor disorder, we recommend a three-stage approach. Firstly patients must be assessed, and given an unambiguous diagnosis with an explanation that helps them see they have a genuine disorder which has the potential for reversibility. Key ingredients are allowing the patient to describe all their symptoms and to explain their ideas about what may be wrong. It should be made clear that the diagnosis is a positive one based on the presence of typical signs (eg Hoover's sign for paralysis, entrainment test for tremor) which in themselves indicate the potential for reversibility. We suggest an approach leaving out the assumption there are psychological stressors in the patient's life that have caused the symptom. Often the symptoms themselves are the main stressor. Insisting that there must be others simply leads to a frustrated doctor and angry patient. Instead, at this first stage we encourage exploration of mechanism, e.g. triggering of symptoms by pain, injury or dissociation and a discussion about how symptoms arise as "abnormal motor programs" in the nervous system.

Secondly, further time spent exploring this diagnosis, treating comorbidity and, in the context of a multidisciplinary team, trying out altered movements and behaviors may benefit some patients without the need for more complex intervention.

Thirdly, some patients do require more complex treatment, often with a combination of physical rehabilitation and psychological treatments. Hypnosis, sedation and transcranial magnetic stimulation may have a role in selected patients.

Finally many patients do not respond to treatment, even when they have confidence in the diagnosis. Ultimately however, patients with functional motor disorder may have much greater potential for recovery than health professionals often consider.

INTRODUCTION

Functional (also known as psychogenic) motor disorders encompass weakness or movement disorders (such as tremor, gait disorder or dystonia), that are genuine but do not relate to recognised neurological disease. Symptoms are involuntary and should not be confused with feigning or malingering. The diagnosis should not be one of exclusion but rather based upon positive clinical signs of internal inconsistency. In some cases incongruity with recognised neurological disorder is also important but this is a lesser issue [1;2].

Functional motor disorders (FMD) have a signfiicant impact on both the individual patients and the health care system as a whole. They are the second most common functional neurological disorder seen in outpatient practice [3;4] and account for a substantial number of inpatient admission days [5]. Patients with symptoms unexplained by a recognized neurological disease have similar levels of disability, and more distress than patients with symptoms explained by disease [6]. Case control studies have shown levels of disability and health status comparable to Parkinson's disease [7] and multiple sclerosis [8]. The prognosis of FMD is variable but generally unfavorable [9].

From a historical perspective, the range of treatments in FMD (described as hysteria or conversion disorder at the time), has reflected the many differing hypotheses regarding their origin. These include hysterectomy, hypnosis, suggestion, abreaction, electrical stimulation (of the affected limb), various forms of constrained and other physical rehabilitation, and psychotherapy including psychoanalysis [10-12]. We have largely restricted ourselves to studies since 1965 whilst remaining aware that there are many important lessons to be learnt from older treatments.

In this review we summarize current evidence for treatment of FMD focusing on physiotherapy and psychological treatments [13], but also discussing other treatments such as hypnosis, transcranial magnetic stimulation, sedation and pharmacologic treatment.

Throughout, we would like to emphasize our clinical experience that there is little benefit attempting to embark on treatment before a good initial consultation [1;14]. A patient who has no confidence or understanding of the nature of its diagnosis rarely benefits from the treatments described below. It is our view that the neurologist or diagnosing physician is in a position to deliver the first phase of treatment and

not just the diagnosis. Figure 1 shows a proposal of a 'stepped care' approach in FMD where the neurologist provides 'Step 1' of the treatment, brief therapy [most commonly delivered by a physiotherapist for FMD] can be seen as 'Step 2' and more complex multidisciplinary care involving the full rehabilitation team and psychiatry/ psychology can be seen as 'Step 3' **(see figure 1)**[15].

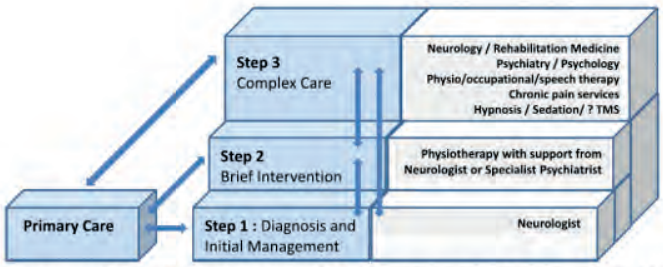


Fig. 1. Stepped care approach for functional motor disorder. Note that patients may need to go back to step 1 from step 2 or 3 if this has not been successful. (*Adapted from* Health Improvement Scotland [15].).

TREATMENT

Physical therapy

Physiotherapy

Patients are often referred for physiotherapy after consulting a neurologist. The emerging evidence supports the idea that, regardless of psychiatric comorbidity, patients with FMD often benefit from an approach in which they are taught about the nature of their abnormal movements and how to move in a more normal way. The most successful programs appear to do this by conceptualizing the FMD as a problem with abnormally learnt 'motor programs' in the brain which have to be 'unlearnt' [13;16]. More data is certainly required, and in particular, there is much work to be done on refining and describing techniques that may be specifically helpful for individual symptoms. Physiotherapists are surprisingly positive about treating this group of patients but feel lacking in knowledge and support from medical colleagues in doing so [17].

The first randomized controlled study of physiotherapy in 60 patients with functional gait disorder (mean duration of symptoms of 9 months), was reported recently by Jordbru et al[16]. The authors compared immediate or delayed inpatient physical rehabilitation without any psychotherapy. The intervention led to a mean 7 point change in a 15 point measure of functional mobility compared to controls waiting for the treatment and a return to normal functional independency in the active treatment group.

A retrospective study of physiotherapy compared 60 patients (mean duration of symptoms 17 months) with 60 patients who had received historical usual care [18]. The one week intervention, like that of Jordbru et al. focused on physical function, with gradual progression from elementary to more complex movements, in combination with only a little psychotherapeutic element [16]. Directly after treatment, 74% were improved according to both physician- and self-rating. At follow-up (median 25 months) 60% had self-rated improved symptoms and 62% mild or no disability level, compared to 22% and 44% respectively in the control group. The main methodological limitation of the comparison is that the control group consisted of those patients who refused to have treatment and so were intrinsically less likely to do well. Nonetheless, even as a retrospective uncontrolled series these data suggest a possible better outcome in chronic FMD than might be expected based on existing literature.

Another study investigated the effect of a thrice-weekly, 12-week mild walking program on mild to moderate functional movement disorders (mean symptom duration 15 months) on 16 patients [19]. Results showed an average of 70% improvement of symptoms in 10 of 16 patients. As no control group was used and symptom duration was short, the intervention effect could be attributed to several factors: there is a social element to group walking therapy since it has been shown that walking improves general wellbeing, improvement could also be attributed to natural history of the disorder, although again the improvement after a long duration is encouraging.

A systematic review of physiotherapy for FMD found a further 25 case series and reports of physiotherapy for FMD with low levels of evidence but nonetheless a trend towards positive outcome [13]. In most studies a behavioral motor learning program was used: positive reinforcement with praise or rewards and privileges, while ignoring abnormal movement and maladaptive behaviors.

Inpatient rehabilitation with combined multidisciplinary treatment

A recent study [20] (n=33, mean duration of symptoms 48 months) used a combination of occupational therapy, focusing on motivation and reinforcement, physiotherapy with posture exercises and massage and psycho-education. 85% of patients received CBT, techniques included 'fostering insight and assertiveness'. Significant improvement was found in MRS scores ($p<0.001$), mobility ($p<0.001$) and ADL ($p=0.002$). No control group was studied.

A retrospective study [21] (n=26, 63% symptom duration > 3 years, all previously received failed treatment) investigated an inpatient intervention consisting of physiotherapy, occupational therapy, cognitive behavioral therapy, neuropsychiatry assessment and neurology input as required. 58% of patients reported benefit from the program on discharge and the same percentage at a mean follow-up of 7 years, but no improvement on employment rate was found. Patients were excluded if they did not accept the rationale for CBT. Thus even in a treatment resistant population, treatment is still possible, although is not suitable for those who do not accept the premise of treatment in the first place.

Contraindications, complications: Patients typically report that exercising exacerbates pain and fatigue which needs to be anticipated as part of therapy.

Cost/Cost effectiveness: No literature is available concerning the cost-effectiveness. Costs depend on treatment duration, which vary highly between studies.

Psychotherapy

The level of available evidence for psychotherapy of FMD is low [22] and much of the suggested emphasis on psychotherapy is based on historical practice or inferred from studies of similar patient populations such as patients with non-epileptic attacks or other functional somatic symptoms.

Psycho-education and explanation

To our knowledge there are no studies specifically focusing on the effectiveness of explanation and education of symptoms in this population. It is however widely believed by many specialists that education is important and can often be an effective treatment strategy [23]. Studies of non-epileptic attacks have shown that around one third of patients will improve with a single consultation [24;25] and prognostic studies of both FMD and non-epileptic attacks suggest that anger with the diagnosis predicts poor outcome [14;26]. Qualitative studies have also reinforced the importance of giving patients tangible diagnoses [27-29]. A combined consultation and written information can be carried out with a high level of patient satisfaction [28].

Most articles on the process of giving the diagnosis of FMD and other functional neurological disorders emphasize the importance of some of the items in Table 1. In fact these are no different to important ingredients of giving a diagnosis for any medical condition.

Where authors diverge is in the name given to the condition and by default the associated explanation. Some deliberately avoid making a diagnosis [30] others emphasize re-learning normal movement [18] as part of a functional explanation. Others may use a more clear cut 'psychogenic' explanation [31]. We know something of which terms patients prefer but this is an area that would benefit from further study [33].The pros and cons of different terms and models of these disorders is discussed elsewhere [32].

Explanations that rely on normal imaging or normal examination are generally not appreciated by patients who want to know what they have got, not what they don't have. For the same reason terms such as 'medically unexplained' tend to be regarded especially negatively.

Combined psychiatric and neurological consultation

One study investigated the effect of a combined consultation of a psychiatrist and a neurologist and a number of subsequent consultations, depending on individual demand (mean 2.8 visits) in 12 patients and 11 control subjects (usual care) [34]. The aim was to explain the functional nature of the symptoms, offer coping strategies and address the potential role of psychological factors. Of the patients from the joint consultation group 83% reported good outcome, compared to 36% of the control group, furthermore this group scored better on SF-12 scale, reported significantly lower symptom severity and sought less medical help.

Element	Example
Give the patient a diagnosis.	"You have a functional movement disorder."
Emphasize that symptoms are genuine (and common).	"Your symptoms are not 'imagined' or 'crazy.'"
Explain on what basis the diagnosis has been made.	e.g., showing patient positive features of the diagnosis such as Hoover's sign or tremor entrainment test
Emphasize potential for reversibility.	"Your Hoover's sign shows us that your leg has the potential to improve."
Emphasize the role of self-help/ education. "	I'd like you to read this information (e.g., www.neurosymptoms.org]. It's not your fault that you have this, but you will need to work at it to get better."

Table 1. Some commonly agreed initial ingredients of a successful explanation of functional neurological symptoms

Cognitive behavioural therapy (CBT)

Cognitive behavioural therapy broadly describes a psychotherapy in which the patient is encouraged to challenge patterns of thinking and behaviour that are creating

obstacles to symptom improvement. It focuses more on perpetuating factors than on predisposing factors. There are no trials of CBT in functional motor disorder, [22;35] although individual case studies report success [36], as do above mentioned studies combining CBT with physical therapy [20;21]. A RCT of a brief guided self-help intervention based on CBT for patients with a variety of functional neurological disorders including FMD demonstrated benefit at 3 months and 6 months in the treatment group [37] with a number needed to treat of 7.

Most studies of CBT for functional disorders show benefit. Even a study of CBT in 'somatisation disorder' was effective [38]. Patients with FMD typically do have many other functional somatic symptoms but we should be cautious about assuming that CBT is necessarily beneficial without more evidence.

Psychodynamic therapy

Psychodynamic therapy generally involves helping the patient to see their symptoms in the context of interpersonal relationships and life narrative. In a randomised trial by Kompoliti et al. (n=15) with early psychodynamic therapy versus three months of monitoring from a neurologist and after that psychodynamic therapy [39], found the same improvement in both groups. This study evolved from a case series of 10 patients of whom 8 improved [40]. Both studies are too small to draw conclusions from although did highlight a high refusal rate for this kind of therapy in a trial setting (60% eligible patients refused).

Reuber et al. also described tailored psychodynamic therapy for 91 patients with functional neurological symptoms including at least 15 with FMD [41]. 49% improved by at least one standard deviation on measures of health status.

Contraindications, complications: It is recognized that psychotherapy can sometimes temporarily worsen FMD, especially when adverse experiences are discussed for the first time.

Costs/ Cost effectiveness: Reuber et al. studied CBT in several functional neurological symptoms, amongst which 15% movement disorders and 12% problems with gait [41]. They estimated a cost per "quality adjusted life year" at £5.328 based on the total study population.

Pharmacologic treatment

Antidepressants

Little has been published on pharmacological treatment of motor symptoms in FMD. No randomized or controlled studies have been conducted. Voon et al. published a series of 15 patients with functional hyperkinetic movement disorders who underwent treatment with different kinds of SSRI's (Selective Serotonin Reuptake Inhibitors) [42]. The study was confounded by concurrent psychotherapy and does not meaningfully contribute to the evidence regarding antidepressant use.

Contra-indications and side effects, other than those that are known, of the use of an SSRI in this specific patient group are not known. Based on present literature there is no evidence to support efficacy of any pharmacological treatment for the motor symptoms of FMD. However it is reasonable to consider antidepressants for other common symptoms in FMD such as pain, insomnia, anxiety and depression.

Interventional procedures

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive method by which electromagnetic induction is used to explore cortical excitability and connectivity. Repetitive TMS (rTMS) can generate long-term potentiation or depression. TMS has been widely used in neurological and psychiatric disorders as a tool to gain insight into pathophysiology as well as a possible therapeutic treatment [43;44]. Abnormalities in cortical excitability have been found in functional limb weakness [45;46] although it may be that these changes are similar to those found in volunteers feigning [47].

A systematic review has been conducted on the effectiveness of TMS and rTMS in FMD which explored the quality and limitations of seven studies [48]. Combining this with one subsequent study means there are uncontrolled data on 119 patients who have received TMS treatment (78 weakness, 41 movement disorder) [49].

The publications are dominated by two French studies both reporting successful outcomes. Chastan and Parain's retrospectively studied the use of rTMS delivered over a single 2-3 minute period in the hemisphere contralateral to the weakness to 70 patients with functional limb weakness [50]. In this highly acute and young group (44 of whom were under 20 years of age with a median duration of 5 days) there was a 89% recovery either immediately or within days. It recurred in some but repeated treatment was reported as effective. The study by Garcin et al. was from

a different centre and also reported single session TMS treatment in a group of 24 with movement disorder of much longer duration (2.8 years) [49]. 75% of the patients improved by more than 50% immediately after TMS with 6 patients experiencing complete resolution. The patients then received physiotherapy, psychology and neurology follow up and were assessed at a median duration of 20 months later. At that point 71% of patients were much improved. Both studies used a stimulus sufficient to induce movement in the limb. Only one study had negative findings [51].

From a methodological perspective these studies do suggest that TMS may be a useful treatment for FMD but we should be careful to jump into too many conclusions. Patients with acute FMD may improve anyway, especially if acute, and the results in the patients from the Garcin study may have been influenced by subsequent therapy from an interested team [49]. The only study with negative results was not published so far and included patients with chronic symptoms [51]. Authors have argued that TMS can induce changes in cortical excitability [50], whereas others have pointed out that the duration of the TMS stimulus is not sufficient to induce a long lasting physiological change in the brain [48;49]. Alternative possibilities are a placebo effect, 'relearning', regaining function with a treatment that is acceptable to the patient and/or facilitating insight in the disorder. Garcin et al. described it as a "cognitive-behavioral effect when patients see an unexpected alteration of their movement disorder. This, combined with suggestion, could be a powerful stimulus inducing change in belief about symptoms and could trigger or help recovery"[49]. It certainly warrants further evaluation in controlled studies.

Contraindications, complications: TMS is considered a safe therapy, although seizures have been reported sporadically, the risk is considered very low [52].

Cost/Cost effectiveness: No literature is available on the costs or cost-effectiveness.

Transcutaneous Electrical Nerve Stimulation / Peripheral Stimulation.

Transcutaneous Electrical Nerve Stimulation (TENS) refers to a treatment concerning low-voltage electrical currents applied to the skin. Although there is no consensus on the optimal paradigm nor the mechanism of action, it is a widely used treatment in acute and chronic pain. Studies have been published with positive results using TENS in other movement disorders [53-55], little is known of its efficacy in FMD.

Literature on TENS in FMD consists of case reports or small case series [56-61]; and one larger study [62] in which 19 patients with various functional movement

disorders underwent a trial of TENS therapy. Electrodes were placed on the muscles most affected. All patients who considered the trial effective were offered daily TENS treatment during 30 minutes. Results showed that 15 patients (79%) chose to continue TENS after 4 months, although only 5 demonstrated a clear (>50%) effect on blindly assessed standardized videotapes, or phone assessment (42%). Shorter duration of symptoms was associated with better outcome. Because of the small population, study design, lack of a control or use of placebo no firm conclusions can be drawn on efficacy of this treatment strategy, but like TMS it may have a place in the context of rehabilitation.

Electrical stimulation of muscles using functional electrical stimulation (which produces more of a muscle jerk than TENS) has been reported in a case report [63]. Varieties of electrical stimulation were common practice as a treatment for FMD in the late 19th and early 20th century and were frequently reported to be successful. EMG feedback has also been reported successfully in four patients which may involve similar mechanism when successful [64].

Contraindications, complications: in the study by Ferrara et al. two patients temporarily got worse. TENS is generally considered a safe therapy, contra-indications include patients with an Implantable Cardioverter-defibrillator (ICD) [65].

Cost/Cost effectiveness: no literature is available on the costs or cost-effectiveness.

Abreaction and Sedation

Abreaction describes a psychiatric interview carried out while the patient is deliberately sedated. The original purpose of this was, in psychoanalytic terms, to access hidden memories, induce catharsis and thus resolve the hypothesized conflict underlying the symptom. A review summarized studies of abreaction for functional neurological disorders (33% FMD) [12]. The effect was often positive, but none of the 55 included studies (mainly older case reports or case series) had a (placebo) control group.

Stone et al described the effects of sedation with the anaesthetic propofol on 11 patients with severe FMD median duration 14 months who had already accessed multidisciplinary treatment and explanation [66]. The rationale here was to use sedation to demonstrate reversibility of symptoms to the patient in situations where this was not possible using the normal consultation (ie fixed dystonia, mutism). A case report of a woman with chronic bilateral upper limb functional dystonia showed

the same effect, with complete (temporary) disappearance of dystonia during short propofol induced narcosis [67]. Five patients experienced rapid resolution or major improvement of their symptoms. These studies are subject to the same criticism as other case series but the effect was not confounded by other new treatments and the patients largely had chronic symptoms.

Acupuncture

Although acupuncture is widely studied in other functional disorders only one case report was found in English literature [68] on a patient with longstanding functional myoclonus, who responded to acupuncture. The authors contemplate a placebo effect to explain the results. In the Chinese literature there are other reports of acupuncture for FMD including one paper describing a 99% success rate in 1316 patients with functional paralysis [69].

Other therapies

Suggestion / Placebo

Placebo and suggestion cover a wide variety of potential treatments, ranging from an inert pill or infusion, to simply suggesting to the patient they may get better. The latter could be said to be a very simple form of cognitive therapy and as such is not really placebo. This may explain why placebo performs so differently among different studies.

One study with saline infusion and one case report with a placebo pill in FMD found respectively improvement in 7 of 12 patients at follow-up (duration not stated), and complete recovery [70;71].

Edwards et al report immediate resolution of symptoms of botulinum in three patients with fixed dystonia [72]. As the authors discussed, had to be consistent with a placebo effect since botulinum only becomes active after 72 hours. The authors sound a note of caution about the use of this treatment but it nonetheless deserves consideration in patients where improvement by other means is not possible.

Neurologists who value transparency and honesty in diagnosis and treatment of FMD naturally object to the idea of deceptive placebo. There is a counter argument however. Placebo could be especially beneficial in functional disorders, since they may share similar pathways [73] and may be associated with similar activity of brain regions found in fMRI-studies [74]. Furthermore deception is not necessary to achieve a placebo effect [75] and patients might not reject placebo use [76]. Placebo

response is of course an issue for many disorders in medicine and the topic is certainly an important one to consider in the design of trials.

Deliberate restriction of activity or deception by the doctor.

Several earlier studies report on strategies to motivate patients recovery by restricting their activity or use of facilities [77;78]. In a series of papers Shapiro and Teasell described a paradoxical rehabilitation technique in which patients were told that their symptoms would be purely psychiatric if they did not improve [79;80]. The authors report improvement (71% of 23 patients improved or remitted at discharge) but we cannot endorse an approach which deliberately sets out to deceive patients and are doubtful that it would lead to long lasting improvements. Likewise deliberate restriction of facilities or enforced disability is not compatible with modern clinical practice.

Hypnosis

Hypnosis has been used widely for FMD since the 19th century. Studies of hypnotic models of FMD have highlighted similarities to patients with clinical FMD [81;82]. Hypnosis was studied in a randomized controlled trial (RCT) as an addition to standard inpatient treatment with multidisciplinary physical and psychological therapy in 92 patients with FMD [83]. There was impressive symptom reduction in both groups suggesting benefit from multidisciplinary treatment but no additional benefit from hypnosis.

In another RCT the effect of ten sessions of hypnosis on 44 outpatients with long duration FMD was studied (median 3.7 years) [84]. Patients improved highly significantly compared with a waiting list control group after with before treatment.

Separating out the specific effects of hypnosis from other elements of the consultation is probably impossible but the technique almost certainly has a useful role in some patients.

Complications and contraindications: Hypnosis and placebo, in common with all treatments for FMD, run the risk of nocebo, that is the possibility that the patient responds negatively to the suggestions and develops worsening symptoms.

Cost / cost effectiveness; No literature is available on the costs, nor the cost-effectiveness of above mentioned therapies.

Emerging therapies

This review of existing studies highlights the relatively low quality of most studies and lack of randomized designs. There are particular challenges in designing treatment trials for patients with FMD. These range from how to deal with a 'placebo' arm when placebo may be an effective and desirable treatment to the difficulty of finding outcome measures that capture improvement in patients who are often polysymptomatic. Building an evidence base for a multimodal and stepped approach to treatment of FMD does remain possible. Trial registers indicate ongoing interest in TMS, psychotherapy in functional movement disorders and YD and MT are currently conducting a trial investigating botulinum-toxin injections in functional jerky movements.

Treatment of Pediatric FMD

The course of functional motor disorder in children is often thought to be benign, but data is limited and in some studies school absence, disability and morbidity is high [85]. It seems likely that many of the same factors that are associated with adult FMD can be translated in to the pediatric disorder. Several small uncontrolled studies have examined the effect of a multidisciplinary approach involving neurology, psychiatry, and social work/psychology [86], with good results . All studies underline the importance of family involvement in the treatment.

COMPLIANCE WITH ETHICS GUIDELINES

Conflict of Interest

Jeannette M. Gelauff has received grant support from a BCN Groningen Scholarship.

Yasmine E.M. Dreissen has received grant support from the Princess Beatrix Fund for a trial on botulinum toxin in functional jerky movement disorders. This money was paid to the AMC Medical Research BV in Amsterdam (Yasmine E.M. Dreissen's salary is paid from this money). She has also had travel expenses paid by the Princess Beatrix Fund, and Ipsen Pharmaceuticals paid partially for the botulinum toxin used in the trial.

Marina A.J. Tijssen has received grant support from STW Technology Society (NeuroSIPE), Netherlands Organization for Scientific Research (NWO Medium), Fonds Nuts-Ohra, the Princess Beatrix Fund, the Gossweiler Foundation, Stichting Wetenschapsfonds Dystonie Vereniging, Ipsen, Allergan, and Medtronic. The

money was paid to the university (University of Amsterdam and from 2012 onwards Rijksuniversiteit Groningen).

Jon Stone has received grant support from the NHS Scotland National Research Strategy Career Fellowship and the NIHR (as principal investigator); is employed by NHS Lothian; has regularly provided medicolegal expert witness testimony for negligence and personal injury cases; has received lecture honoraria from St. Louis Neurology, UK Tribunals Judiciary, Iceland Neurology Department (UCB), the Portuguese Movement Disorders (Novartis), Cork Neurology (UCB), the Movement Disorders Society, and the St. Louis Neurology Department; has received royalties from UpToDate; has had travel expenses covered for lecturing by BMA, Royal College of Physicians, the European Neuro-ophthalmology Society, the Movement Disorders Society, the European Neurological Society, the Iceland Neurology Department, and the Cork Neurology Department; and runs a free self-help website for patients with functional motor disorders (www.neurosymptoms.org) mentioned in this article.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

REFERENCES

1. ***Stone J, Edwards M. Trick or treat? Showing patients with functional (psychogenic) motor symptoms their physical signs. Neurology 2012 Jul 17;79(3):282-4**.

   Based on clinical experience, the authors argue the value of actually showing patients the positive signs of their diagnosis (eg Hoovers sign or entrainment test) to persuade patients of the accuracy and reversibility of the disorder, to signs in the explanation.

2. Kanaan R, Armstrong D, Wessely S. Limits to truth-telling: neurologists' communication in conversion disorder. Patient Educ Couns 2009;77(2):296-301.
3. Stone J, Carson A, Duncan R, Roberts R, Warlow C, Hibberd C, et al. Who is referred to neurology clinics?--the diagnoses made in 3781 new patients. Clin Neurol Neurosurg 2010;112(9):747-51.
4. Lempert T, Dieterich M, Huppert D, Brandt T. Psychogenic disorders in neurology: Frequency and clinical spectrum. Acta Neurologica Scandinavica 82(5):335-40
5. Parry AM, Murray B, Hart Y, Bass C. Audit of resource use in patients with non-organic disorders admitted to a UK neurology unit. J Neurol Neurosurg Psychiatry 2006;77(10):1200-1.
6. Carson A, Stone J, Hibberd C, Murray G, Duncan R, Coleman R, et al. Disability, distress and unemployment in neurology outpatients with symptoms 'unexplained by organic disease'. J Neurol Neurosurg Psychiatry 2011;82(7):810-3.
7. Anderson KE, Gruber-Baldini AL, Vaughan CG, Reich SG, Fishman PS, Weiner WJ, et al. Impact of psychogenic movement disorders versus Parkinson's on disability, quality of life, and psychopathology. Movement Disorders 2007; 22(15):2204-9
8. Stone J, Sharpe M, Rothwell PM, Warlow CP. The 12 year prognosis of unilateral functional weakness and sensory disturbance. J Neurol Neurosurg Psychiatry 2003;74(5):591-6.
9. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. J Neurol Neurosurg Psychiatry 2013 Sep 12. doi: 10.1136/jnnp-2013-305321
10. Bogousslavsky J. Hysteria after Charcot: back to the future. Front Neurol Neurosci 2011;29:137-61.
11. Splett T, Steinberg H. Treatment of hysteria in the 19th century--in which way did German psychiatrists view castration? Fortschr Neurol Psychiatr 2003;71(1):45-52.
12. Poole NA, Wuerz A, Agrawal N. Abreaction for conversion disorder: systematic review with meta-analysis. Br J Psychiatry 2010;197(2):91-5.
13. ***Nielsen G, Stone J, Edwards MJ. Physiotherapy for functional (psychogenic) motor symptoms: A systematic review. Journal of Psychosomatic Research 2013;75(2):** 93-102. doi: 10.1016/j.jpsychores.2013.05.006

    A systematic review of physiotherapy for FMD , showing a trend towards positive outcome, although evidence is limited.

14. Stone J, Carson AJ, Scharpe M. Psychogenic movement disorders: explaining the diagnosis. Psychogenic Movement Disorders and Other Conversion Disorders. Cambridge: Cambridge University Press; 2011. p. 254-66.
15. Health Improvement Scotland. (2012). *Stepped care for functional neurological symptoms*. HS Scotlland, Edinburgh. http://www.healthcareimprovementscotland.org/our_work/long_term_conditions/neurological_health_services/neurological_symptoms_report.aspx (accessed Dec 21 2013)

16. *Jordbru AA, Smedstad LM, Klungsoyr O, Martinsen EW. Psychogenic gait disorder: A randomized controlled trial of physical rehabilitation with one-year follow-up. J Rehabil Med 2013 Nov 13. doi: 10.2340/16501977-1246

The first randomised study of physiotherapy in FMD: An intervention of physical rehabilitation in a cognitive behavioural framework in 60 patients with FMD obtained positive results.

17. Edwards MJ, Stone J, Nielsen G. Physiotherapists and patients with functional (psychogenic) motor symptoms: A survey of attitudes and interest. Journal of Neurology, Neurosurgery and Psychiatry 2012;83(6):655-8

18. * Czarnecki K, Thompson JM, Seime R, Geda YE, Duffy JR, Ahlskog J. Functional movement disorders: Successful treatment with a physical therapy rehabilitation protocol. Parkinsonism Relat Disord 2012;18(3):247-51

A retrospective study to a one week physical therapy intervention suggesting a promising outcome of chronic FMD.

19. Dallocchio C, Arbasino C, Klersy C, Marchioni E. The effects of physical activity on psychogenic movement disorders. Movement Disorders 2010;25(4): 421-5

20. McCormack R, Moriarty J, Mellers JD, Shotbolt P, Pastena R, Landes N, et al. Specialist inpatient treatment for severe motor conversion disorder: a retrospective comparative study. J Neurol Neurosurg Psychiatry 2013 Oct 11. doi: 10.1136/jnnp-2013-305716

21. Saifee TA, Kassavetis P, Parees I, Kojovic M, Fisher L, Morton L, et al. Inpatient treatment of functional motor symptoms: A long-term follow-up study. Journal of Neurology 2012;259(9):1958-63

22. Ruddy R, House A. Psychosocial interventions for conversion disorder. Cochrane Database Syst Rev 2005;(4):CD005331.

23. Espay AJ, Goldenhar LM, Voon V, Schrag A, Burton N, Lang AE. Opinions and clinical practices related to diagnosing and managing patients with psychogenic movement disorders: An international survey of movement disorder society members. Movement Disorders 2009;24(9) :1366-74

24. McKenzie P, Oto M, Russell A, Pelosi A, Duncan R. Early outcomes and predictors in 260 patients with psychogenic nonepileptic attacks. Neurology 2010;74(1):64-9.

25. Razvi S, Mulhern S, Duncan R. Newly diagnosed psychogenic nonepileptic seizures: health care demand prior to and following diagnosis at a first seizure clinic. Epilepsy Behav 2012;23(1):7-9.

26. Carton S, Thompson PJ, Duncan JS. Non-epileptic seizures: patients' understanding and reaction to the diagnosis and impact on outcome. Seizure 2003;12(5):287-94.

27. Baxter S, Mayor R, Baird W, Brown R, Cock H, Howlett S, et al. Understanding patient perceptions following a psycho-educational intervention for psychogenic non-epileptic seizures. Epilepsy Behav 2012;23(4):487-93.

28. Hall-Patch L, Brown R, House A, Howlett S, Kemp S, Lawton G, et al. Acceptability and effectiveness of a strategy for the communication of the diagnosis of psychogenic nonepileptic seizures. Epilepsia 2010;51(1):70-8.

29. Salmon P, Peters S, Stanley I. Patients' perceptions of medical explanations for somatisation disorders: qualitative analysis. BMJ 1999;318(7180):372-6.

30. Friedman JH, LaFrance W. Psychogenic disorders: The need to speak plainly. Archives of Neurology 2010;67(6):753-5

31. Duncan R. Psychogenic nonepileptic seizures: diagnosis and initial management. Expert Rev Neurother 2010;10(12):1803-9.

32. Edwards, M. J., Stone, J., & Lang, A. (2013). From Psychogenic Movement Disorder (PMD) to Functional Movement Disorder (FMD): It's time to change the name. Movement Disorders, I2013 Jul 10. doi: 10.1002/mds.25562

33. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, et al. What should we say to patients with symptoms unexplained by disease? The "number needed to offend". BMJ 2002;325(7378):1449-50.

34. Aybek S, Hubschmid M,Mossinger C, Berney A, Vingerhoets F. Early intervention for conversion disorder: neurologists and psychiatrists working together. Acta Neuropsychiatrica 2012. DOI: 10.1111/j.1601-5215.2012.00668.x

35. Hopp JL, LaFrance WC, Jr. Cognitive behavioral therapy for psychogenic neurological disorders. Neurologist 2012;18(6):364-72.

36. Baslet G, Hill J. Case report: Brief mindfulness-based psychotherapeutic intervention during inpatient hospitalization in a patient with conversion and dissociation. Clinical Case Studies 2011;10(2):95-109

37. Sharpe M, Walker J, Williams C, Stone J, Cavanagh J, Murray G, et al. Guided self-help for functional (psychogenic) symptoms: a randomized controlled efficacy trial. Neurology 2011;77(6):564-72.

38. Allen LA, Woolfolk RL, Escobar JI, Gara MA, Hamer RM. Cognitive-behavioral therapy for somatization disorder: a randomized controlled trial. Arch Intern Med 2006;166(14):1512-8.

39. Kompoliti K, Wilson B, Stebbins G, Bernard B, Hinson V. Immediate vs. delayed treatment of psychogenic movement disorders with short term psychodynamic psychotherapy: Randomized clinical trial. Parkinsonism Relat Disord 2013 Sep 22. doi: 10.1016/j.parkreldis.2013.09.018

40. Hinson VK, Weinstein S, Bernard B, Leurgans SE, Goetz CG. Single-blind clinical trial of psychotherapy for treatment of psychogenic movement disorders. Parkinsonism and Related Disorders 2006;12(3):177-80

41. Reuber M, Burness C, Howlett S, Brazier J, Grunewald R. Tailored psychotherapy for patients with functional neurological symptoms: a pilot study. J Psychosom Res 2007 Dec;63(6):625-32.

42. Voon V, Lang AE. Antidepressant treatment outcomes of psychogenic movement disorder. Journal of Clinical Psychiatry 2005;66(12):1529-34.

43. Edwards MJ, Talelli P, Rothwell JC. Clinical applications of transcranial magnetic stimulation in patients with movement disorders. Lancet Neurol 2008;7(9):827-40.

44. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 2010;71(7):873-84.

45. Geraldes R, Coelho M, Rosa M, Severino L, Castro J, de Carvalho M. Abnormal transcranial magnetic stimulation in a patient with presumed psychogenic paralysis. J Neurol Neurosurg Psychiatry 2008;79(12):1412-3.

46. Liepert J, Hassa T, Tuscher O, Schmidt R. Motor excitability during movement imagination and movement observation in psychogenic lower limb paresis. Journal of Psychosomatic Research 2011;70(1):59-65.

47. Liepert J, Shala J, Greiner J. Electrophysiological correlates of disobedience and feigning-like behaviour in motor imagery. Clin Neurophysiol 2013 Oct 12. doi: 10.1016/j.clinph.2013.09.013

48. Pollak TA, Nicholson TR, Edwards MJ, David AS. A systematic review of transcranial magnetic stimulation in the treatment of functional (conversion) neurological symptoms. J Neurol Neurosurg Psychiatry 2013 Jan 8. Doi:10.1007/s13311-013-0246-x

49. *__Garcin B, Roze E, Mesrati F, Cognat E, Fournier E, Vidailhet M, et al. Transcranial magnetic stimulation as an efficient treatment for psychogenic movement disorders. J Neurol Neurosurg Psychiatry 2013;84(9):1043-6__

A study of 24 patients with functional movement disorders who were treated with a single session TMS and blindly assessed by means of video recordings.

50. Chastan N, Parain D. Psychogenic paralysis and recovery after motor cortex transcranial magnetic stimulation. Movement Disorders 2010;25(10):1501-4
51. Shah BB, Zurowski M, Chen R, et al. Failure of motor cortex repetitive transcranial magnetic stimulation (rTMS) combined with suggestion in the treatment of chronic psychogenic movement disorders (PMDs): a pilot study. 15th International Congress of Parkinson's Disease and Movement Disorders, Toronto, ON, Canada, 2011.
52. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008-39.
53. Toglia JU, Izzo K. Treatment of myoclonic dystonia with transcutaneous electrical nerve stimulation. Ital J Neurol Sci 1985;6(1):75-8.
54. Bending J, Cleeves L. Effect of electrical nerve stimulation on dystonic tremor. Lancet 1990;336(8727):1385-6.
55. Tinazzi M, Farina S, Bhatia K, Fiaschi A, Moretto G, Bertolasi L, et al. TENS for the treatment of writer's cramp dystonia: a randomized, placebo-controlled study. Neurology 2005;64(11):1946-8.
56. Maltete D, Verdure P, Roze E, Vidailhet M, Apartis E, Bellow F, et al. TENS for the treatment of propriospinal myoclonus. Mov Disord 2008;23(15):2256-7.
57. Foley-Nolan D, Kinirons M, Coughlan RJ, O'Connor P. Post whiplash dystonia well controlled by transcutaneous electrical nervous stimulation (TENS): case report. J Trauma 1990;30(7):909-10.
58. Withrington RH, Wynn Parry CB. Rehabilitation of conversion paralysis. J Bone Joint Surg Br 1985;67(4):635-7.
59. Atan C, Seckin U, Bodur H. Hysterical paralysis. Rheumatology International 2007; 27(9):873-4
60. Wojtecki L, Groiss S, Scherfeld D, Albrecht P, Pollok B, Elben S, et al. Transient improvement of psychogenic (proprio-)spinal-like myoclonus to electrical nerve stimulation. Movement Disorders 2009;24(13):2024-5.
61. Brierley H. The treatment of hysterical spasmodic torticollis by behaviour therapy. Behaviour research and therapy 1967;5(2):139-42.
62. Ferrara J, Stamey W, Strutt AM, Adam OR, Jankovic J. Transcutaneous electrical stimulation (TENS) for psychogenic movement disorders. The Journal of neuropsychiatry and clinical neurosciences 2011;23(2):141-8.
63. Khalil TM, Abdel-Moty E, Asfour SS, Fishbain DA, Rosomoff RS, Rosomoff HL. Functional electric stimulation in the reversal of conversion disorder paralysis. Archives of Physical Medicine and Rehabilitation 1988;69(7):545-7.
64. Fishbain DA, Goldberg M, Khalil TM, Asfour SS, Abdel-Moty E, Meagher B, et al. The utility of electromyographic biofeedback in the treatment of conversion paralysis. The American journal of psychiatry 1988;145(12):1572-5.
65. Simpson PM, Fouche PF, Thomas RE, Bendall JC. Transcutaneous electrical nerve stimulation for relieving acute pain in the prehospital setting: a systematic review and meta-analysis of randomized-controlled trials. Eur J Emerg Med 2013 Jul 7. DOI: 10.1097/MEJ.0b013e328363c9c1
66. Stone J, Hoeritzauer I, Brown K, Carson A. Therapeutic sedation for functional (psychogenic) neurological symptoms. Journal of Psychosomatic Research 2013. doi.org/10.1016/j.jpsychores.2013.10.003.

67. Medlin F, Aybek S, Berney A, Guedj E, Delaloye AB, Prior JO, et al. Psychogenic tetraparesis and bilateral upper limb dystonia, regressive under short propofol-induced sedation and during hepatic encephalopathy. Psychosomatics. 2012;53(5):485-8.

68. Van Nuenen BFL, Wohlgemuth M, Wong Chung RE, Abdo WF, Bloem BR. Acupuncture for psychogenic movement disorders: Treatment or diagnostic tool? Movement Disorders 2007;22(9):1353-5..

69. Zhang ZY, Yuan YM, Yan BW, Tian YQ, Wang W, Fan LM. An observation of 1316 cases of hysterical paralysis treated by acupuncture. J Tradit Chin Med 1987 Jun;7(2):113-5.

70. Monday K, Jankovic J. Psychogenic myoclonus. Neurology 1993;43(2):349-52.

71. Baik JS, Han SW, Park JH, Lee MS. Psychogenic paroxysmal dyskinesia: The role of placebo in the diagnosis and management. Movement Disorders 2009;24(8):1244-5.

72. Edwards MJ, Bhatia KP, Cordivari C. Immediate response to botulinum toxin injections in patients with fixed dystonia. Mov Disord. 2011 Apr;26(5):917-8

73. Shamy MCF. The treatment of psychogenic movement disorders with suggestion is ethically justified. Movement Disorders 2010;25(3):260-4.

74. Rommelfanger KS. Opinion: A role for placebo therapy in psychogenic movement disorders. Nature Reviews Neurology 2013;9(6):351-6.

75. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One 2010;5(12):e15591

76. Lynoe N, Mattsson B, Sandlund M. The attitudes of patients and physicians towards placebo treatment--a comparative study. Soc Sci Med 1993;36(6):767-74.

77. Dickes RA. Brief therapy of conversion reactions: an in-hospital technique. Am J Psychiatry 1974;131(5):584-6.

78. Trieschmann RB, Stolov WC, Montgomery ED. An approach to the treatment of abnormal ambulation resulting from conversion reaction. Arch Phys Med Rehabil 1970;51(4):198-206.

79. Shapiro AP, Teasell RW. Behavioural interventions in the rehabilitation of acute v. chronic non-organic (conversion/factitious) motor disorders. Br J Psychiatry 2004;185:140-6.

80. Teasell RW, Shapiro AP. Strategic-behavioral intervention in the treatment of chronic nonorganic motor disorders. Am J Phys Med Rehabil 1994;73(1):44-50.

81. Ward NS, Oakley DA, Frackowiak RS, Halligan PW. Differential brain activations during intentionally simulated and subjectively experienced paralysis. Cogn Neuropsychiatry 2003;8(4):295-312.

82. Bell V, Oakley DA, Halligan PW, Deeley Q. Dissociation in hysteria and hypnosis: evidence from cognitive neuroscience. J Neurol Neurosurg Psychiatry 2011;82(3):332-9.

83. Moene FC, Spinhoven P, Hoogduin KAL, Van Dyck R. A randomised controlled clinical trial on the additional effect of hypnosis in a comprehensive treatment programme for in-patients with conversion disorder of the motor type. Psychotherapy and Psychosomatics 2002;71(2):66-76.

84. Moene FC, Spinhoven P, Hoogduin KA, van DR. A randomized controlled clinical trial of a hypnosis-based treatment for patients with conversion disorder, motor type. Int J Clin Exp Hypn 2003;51(1):29-50.

85. Ferrara J, Jankovic J. Psychogenic movement disorders in children. Mov Disord 2008 Oct 15;23(13):1875-81.

86. Faust J, Soman TB. Psychogenic movement disorders in children: Characteristics and predictors of outcome. Journal of Child Neurology 2012;27(5):610-4.

Chapter 10.

Self-Help information and education using the Internet for motor Functional Neurological Disorder (FND) - A Randomized Controlled Trial (SHIFT).

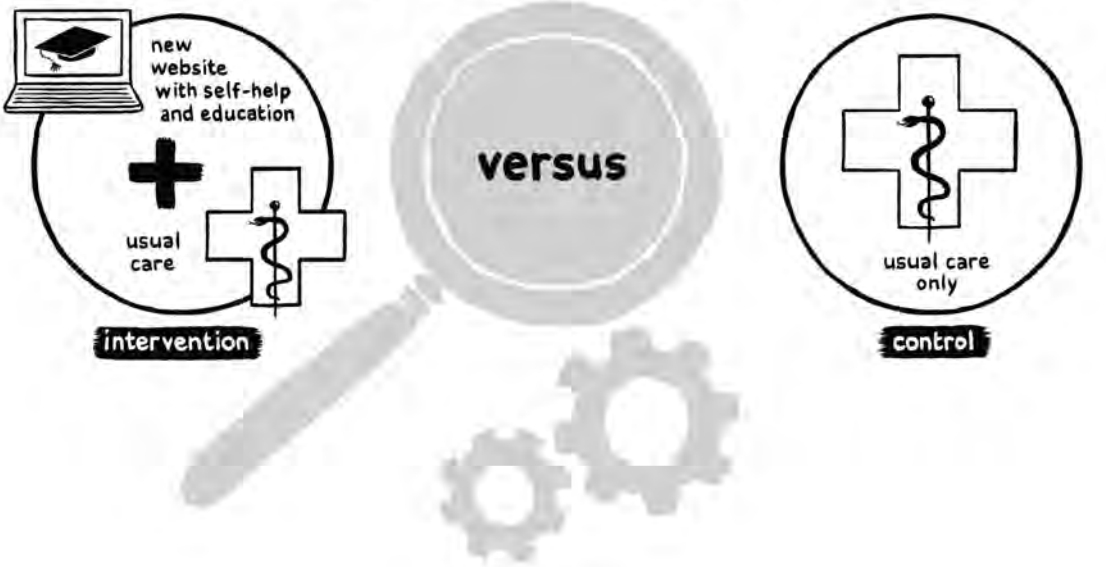
Gelauff JM, Rosmalen JG, Carson A, Dijk JM, Ekkel M, Nielsen G, Stone J*, Tijssen MAJ*.

*Cosignatories**
Trial registry: NCT02589886
Revised Version accepted in Neurology 2020.

10. Does a self-help and education website improve the self-rated health status in patients with functional motor disorders?

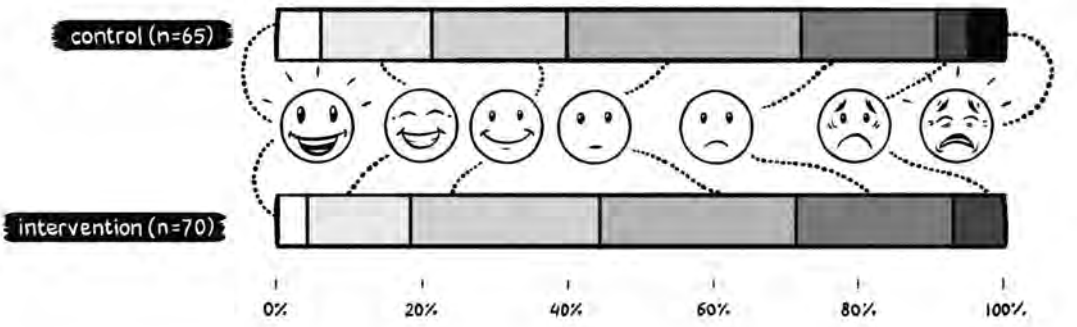
METHODS

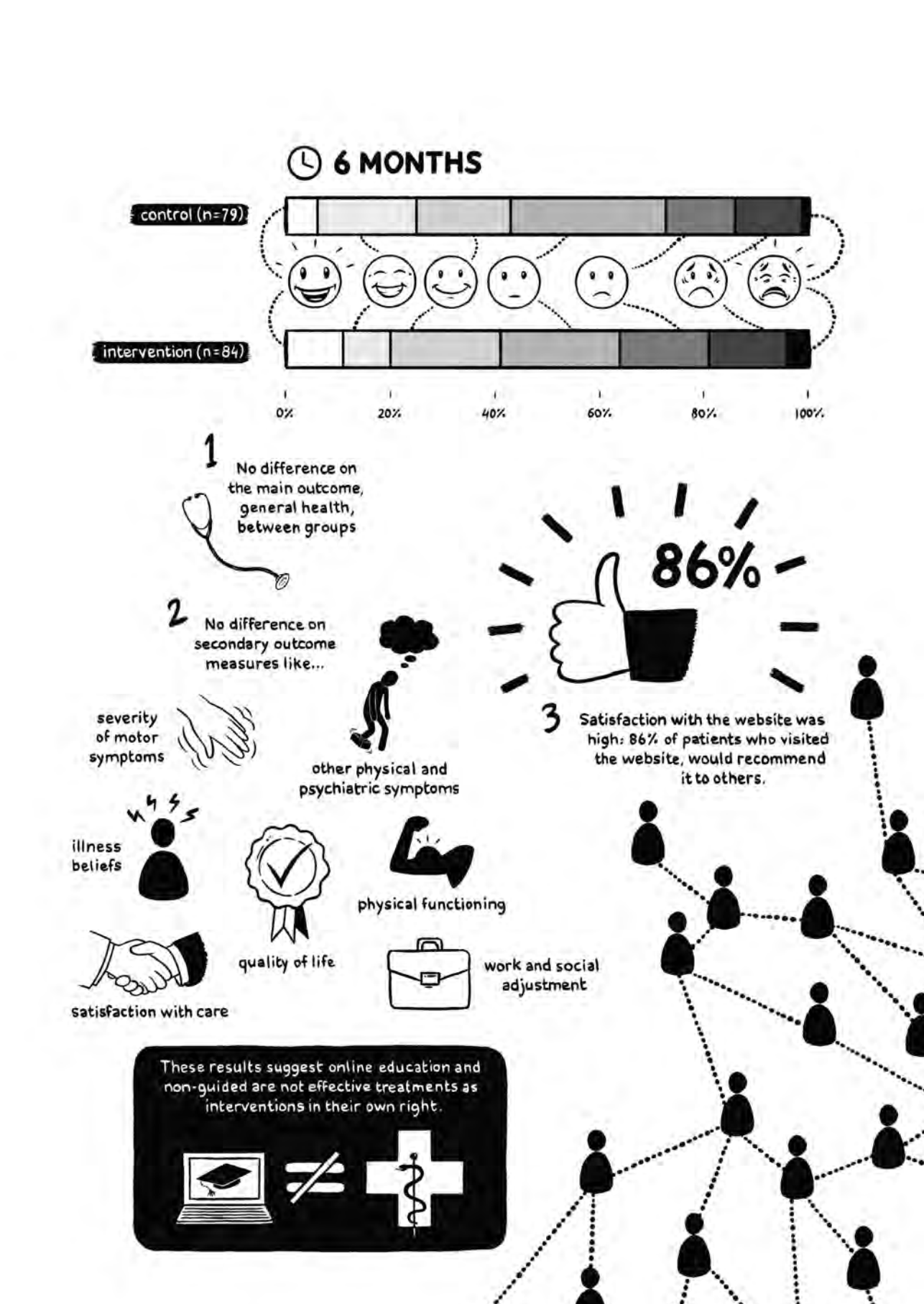
186 patients were randomised in two groups, with a follow-up rate of 87% at 6 months



RESULTS

3 MONTHS




6 MONTHS
control (n=79)
intervention (n=84)
0%
20%
40%
60%
80%
100%
1
No difference on the main outcome, general health, between groups
2
No difference on secondary outcome measures like...
severity of motor symptoms
other physical and psychiatric symptoms
illness beliefs
quality of life
physical functioning
satisfaction with care
work and social adjustment
86%
3
Satisfaction with the website was high: 86% of patients who visited the website, would recommend it to others.
These results suggest online education and non-guided are not effective treatments as interventions in their own right.

ABSTRACT

Background: Explanation of the diagnosis has been suggested as the first step in the approach to motor Functional Neurological Disorder (FND). In this randomised trial we investigated if an online education and self-help intervention, added to usual care, would improve self-rated health in motor FND.

Methods: Patients were 1:1 allocated to an unguided education and self-help website in addition to usual care, or usual care only. Patients over 17 years of age with a functional motor symptom which caused distress or disability were included. The primary outcome was self-rated health on the Clinical Global Improvement (CGI) scale, at three and six months. Secondary outcomes were severity of motor symptoms, other physical and psychiatric symptoms, physical functioning, quality of life, work and social adjustment, illness beliefs and satisfaction with care.

Results: 186 patients were randomised, with a follow-up rate of 87% at 6 months. There was no difference in improvement of self-rated health at three months (44% vs 40%, p=0.899) or six months (42% vs 43%, p=0.435). Secondary outcomes did not differ between groups with a threshold of $p<0.01$. Satisfaction was high, with 86% of patients recommending the website to other patients.

Conclusion: We found no significant effect of the intervention added to usual care on self-rated health or secondary outcome measures, despite high patient satisfaction with the intervention. These results suggest online education and non-guided self-help could be valuable additions to stepped care for motor FND, but are not effective treatments as interventions in their own right.

INTRODUCTION

Expert opinion often suggests that a stepped care approach may be optimal for the treatment of motor Functional Neurological Disorders (FND) as it has the potential to optimise use of health care resources for these common, disabling and persistent disorders. In this context the first important treatment step is the neurologist not just making the diagnosis but explaining the disorder [1, 2]. Good practice statements suggest this should be supported by written information including suitable advice for initial self-management. However, despite enthusiastic advocates, evidence for this approach is lacking. Supporters point to prognostic studies in motor FND [3], dissociative non-epileptic attacks [4, 5] and the broader group of functional neurological symptoms [6], that suggest patient confidence in the diagnosis and the potential to recover is correlated with good outcome. In addition, there are studies that have found improvement in symptoms [7, 8] and high satisfaction with care [9, 10] after explanation of the diagnosis. By contrast, some clinicians express concerns that giving too much information may make symptoms worse and talk about the problem of 'over-medicalisation'. Patient groups have expressed the concern that neurologists might consider self-help as the only required treatment, instead of considering further face-to-face treatment.

We argue that communicating the diagnosis as clearly as possible to patients is a legitimate expectation of any healthcare interaction and it would be unethical not to do so. However, the extent to which supplementing that with online self-help material is beneficial or potentially harmful, is an important but unanswered scientific question.

Within the field of self-help a distinction is generally drawn between 'guided' and 'non-guided' self-help. In guided self-help the patient returns to see a healthcare professional, who monitors progress with the provided information, guides self-help exercises and gives advice. A study that tested such an approach in a more general group of FND patients found modest improvements in the intervention group and no harmful effects [11]. However, although much more widely used, there is far less evidence about unguided self-help, apart from a small number of non-guided interventions in whiplash injury, fibromyalgia and irritable bowel syndrome with mixed results in meta-analysis [12]. No such studies have been performed in FND.

For this study we developed a non-guided web-based programme for use by patients with motor FND. Our model of motor FND was of involuntary motor symptoms

arising from disordered nervous system functioning. This includes changed predictive processing [13], occurring in the context of predisposing, precipitating and perpetuating factors that vary considerably between patients and may be biological, psychological and/or social in nature [14]. Our underlying premise was that the intervention would improve patients' understanding of the disorder and encourage patients to take an active role in their treatment, leading to improvement on clinical meaningful outcomes.

We aimed to test the hypothesis that provision of this website added to usual care, improved the self-rated health status in patients with motor FND compared to usual care only. Our primary outcome was self–rated clinical global improvement with secondary measures of severity of motor symptoms, other physical and psychiatric symptoms, physical functioning, quality of life, and work and social adjustment, illness beliefs and satisfaction with treatment and with the website intervention at three and six months.

METHODS

Study design and procedures

This was a two-group parallel superiority non-blinded randomised controlled trial with patient-rated outcomes at 3 and 6 months. Between October 2015 and July 2017, neurologists from 31 neurology centres across the Netherlands referred eligible patients to the study. These patients were informed about the study by email or post. After giving consent and completing the online baseline questionnaires, patients were randomised into two arms. The intervention group received access to the password-protected unguided education and self-help website as an addition to usual care. They were instructed to read the website at their own pace and preference. The control group received usual care only. 'Usual care' in both groups was not standardised and included any treatment patients received during the trial. Patients were not allowed to discuss medical problems with the investigator after randomisation. This was not violated. All outcome measures were self-report, using online questionnaires at three and six months.

The SHIFT study was performed in accordance with the ethical and legal guidelines of the University Medical Center Groningen (METc 2015/141, M14.150920). All participants gave written consent. The trial was registered at clinicaltrials.gov (NCT02589886).

Participants

Inclusion criteria were (1) 18 years of age or older; (2) functional motor symptom (limb weakness or movement disorder) diagnosed by a neurologist; (3) symptoms causing distress or impairment in social, occupational or other important areas of functioning or warrant medical evaluation (definition according to DMS 5); (4) able to read the Dutch language; and (5) access to a computer with an internet connection on a regular basis. We excluded (1) patients who were unable to provide informed consent; (2) patients with other (functional) complaints, in whom the motor symptom was an accidental finding; and (3) who were known visitors of the (previously available, but during the study offline) translated version of a website by JS (see below). Patients with co-morbid (neurological) disease were not excluded from the study.

Intervention

The tested intervention was a newly developed educational website in Dutch, which included self-help elements. The content was in line with the explanatory biopsychosocial model described by Stone et al [15]. It combined elements of a website developed by JS, www.neurosymptoms.org, a self-help workbook developed for functional neurological symptoms [6] and expert opinion of JS, MT, JR, AC and GN.

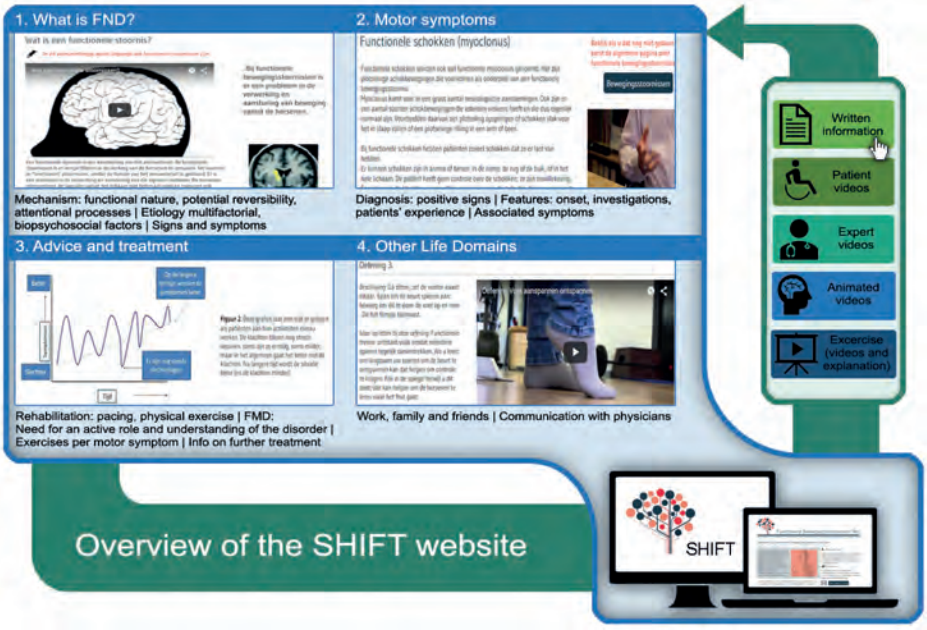


Fig 1. Overview of the non-guided self-help website. Left panel shows examples of pages and descriptions of the content of the four blocks on general FND (1), specific motor symptoms (2) that patients could choose (2), rehabilitation advice, exercises and information on treatment possibilities (3) and on the influence of FND on daily life (4). The right panel shows the different media that were used to provide information, that were mostly newly developed for this study.

The website consisted of four blocks focusing on different domains, and included several different sources of information (figure 1). The website also included exercises adapted from physiotherapy recommendations from Nielsen et al [16].

It was piloted and altered based on the feedback of 12 patients and their family members for intelligibility, clearness, relevance and applicability. Readability scored level B1, with a moderate Douma readability score of 64 out of 100 (based on the English Flesh-Kincaid test), corresponding with a reading age of 13/14 (adjusted for 'functional' and 'disorder').

Outcome Measures

The main outcome was self-rated health, measured on the Clinical Global Improvement (CGI) scale, a seven-point Likert scale (high scores correspond to poor health) at three and six months.

Secondary outcome measures were: severity of all individual motor symptoms (self-rated change in presenting symptom scale (CPS) (range 0-7), fatigue (Checklist Individual Strength (CIS), fatigue severity subscale (range 7-56)), pain (RAND36, the Dutch equivalent of the SF36, subscale (range 0-100)), depressive symptoms (Patient Health Questionnaire-9 (PHQ-9) (range 0-27), anxiety (Generalized Anxiety Disorder Questionnaire (GAD-7; scores 0-14)), health anxiety (Whitely Index (WI-7 range 0-7), health related quality of life and functioning (RAND36) and quality of life (using a single question from the WHO Quality of Life scale "How would you rate your quality of life" (five-point Likert scale, 5 representing good quality of life) (Group, 1998), work and social adjustment (Work and Social Adjustment Scale (WSAS range 0-40)). Illness perception, satisfaction with care and confidence in physiotherapy and psychotherapy were assessed by the level of agreement on a five-point scale on several statements, partly derived from the Illness Perception Questionnaire (IPQ) (see table 1 and 2) and the patient satisfaction questionnaire (PSQ). Additionally, hospitalizations, visits to other websites on FNS and other treatments were recorded. Open fields were available for additional comments, including comments on improvement if that occurred.

A combination of patients' self-report and the number of times they logged on to the website was used to record use of the website. Evaluation of the intervention website was carried out by agreement on a series of statements on a five-point scale (Not at all – strongly agree) (table 3). If patients did not fill out the online questionnaires, they were contacted by phone at 6 months to assess the main outcome, change in

presenting symptoms, quality of life and agreement with the statements 'I would recommend this website to other patients' and 'the website helped me a lot'.

Baseline data from this study was used in another publication on fatigue severity [17].

Sample size

Sample size calculation, using Fisher's exact proportions for independent groups test in G-power version 3.1.7 software, was based on the expected percentage of patients showing any improvement on the CGI self-rated health scale (all scores below 4 'no change'). Based on a previous RCT on self-help [18], our prognosis review [19] and a pilot study of 10 patients in which 40% of patients improved, we estimated that 20% of patients would improve in both groups and an additional 20% in the intervention group. With an alpha of 0.05 and a power of 0.80, a two-tailed calculation resulted in a sample size of 90 patients per group. To anticipate drop out, we aimed for 100 patients per group. No interim analyses were performed.

Randomisation and blinding

Block randomisation with stratification, with a ratio of 1:1 into the intervention and control group, was performed by an online randomisation tool, ALEA, programmed by the Clinical Research Desk of the University Medical Center Groningen. Stratification factors were having limb weakness as a main motor symptom and duration of symptoms > 1 year.

Patients were not blinded to the intervention allocation, because of the obvious difference between the two groups (with and without access to the website). Investigators were not blinded: outcome measures were collected remotely via an online form (with equal procedures in both groups), without interference of the investigator. All research data was anonymised before analysis.

Statistical analysis

An intention to treat analysis was performed at three and six months post randomisation. A *between x within* design was used, by subtracting outcome and baseline values and comparing the differences between groups. Mann-Whitney-U tests (using the whole scale) and Chi-squared tests were used for non-parametric and t-tests for normally distributed variables.

For the main outcome, missing data were imputed, by means of multiple imputation methods using linear regression in SPSS (version23). We imputed missing data

based on all baseline and follow-up variables, generating 5 new datasets. These were used for a sensitivity analysis (to explore the effect of dropout). In the data displayed in tables and outcomes below, data without imputation is provided.

An additional per protocol analysis was planned, excluding patients who never logged on to the website from the intervention group, to investigate if the website itself has a beneficial effect, but would need promotion.

Post-hoc we analysed the effect of *change* between baseline and follow-up on agreement with the statements 'I am confident that the diagnosis functional disorder is correct', 'My disorder is a mystery to me' and 'What I do determines the outcome of my disorder' on the main outcome. Furthermore, we investigated a limited number of possible *prognostic factors* (baseline factors that influence outcome):duration of symptoms, type of referring center (academic vs non-academic), age, gender, and the same illness perception statements as listed above. For these correlations, we used univariable ordinal regression models. First in the entire cohort, and secondly with randomisation group to the model, to investigate if these associations between groups.

Due to multiple comparisons, secondary outcome measures were interpreted conservatively with p values of greater than 0.01 treated with caution.

Data availability statement

Data is available on request from the authors

RESULTS

Participants

355 patients were screened for eligibility, of whom 186 participated in the study. Randomisation resulted in 93 patients for each group at baseline. The flowchart (figure 2) summarizes reasons for exclusion and loss to follow-up.

Reasons for not visiting the website varied. At three months, some patients reported forgetting about it (n=4), believing (n=2) or being concerned (n=2) about undesirable content, alleviated symptoms (n=1), scepticism regarding diagnosis (n=1), and various additional reasons. Between three and six months most patients (n=44) ceased further website visits, primarily due to improved symptoms (n=7), having fully

read the website (n=8), being focused on a different treatment (n=5,); and severe symptoms and/or impaired concentration (n=5). Two patients disagreed with the content citing: dislike of the term 'disorder' and uninformative content; another two 'did not feel like' visiting the site.

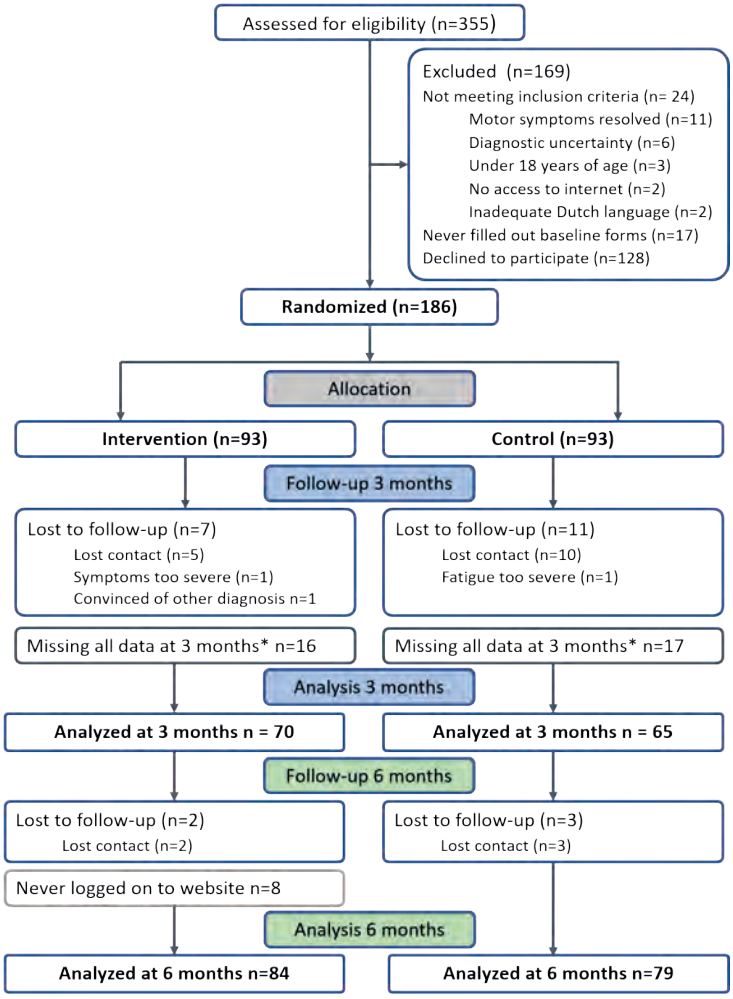


Fig 2. Flow diagram (adapted from CONSORT). *Data was missing at three months, but present at six months (and therefore these participants were not lost to follow-up).

Baseline

The majority of patients were female (72%) and many were out of work (74%), mainly for medical reasons. Mean duration of symptoms was 5.7 years. Self-rated severity of motor symptoms was moderately severe to very severe in 82% of cases. A majority of patients reported confidence that the diagnosis of a functional movement

disorder was correct (62%), however 54% felt the disorder was a mystery to them. Patients reported poor quality of life (only 30% had good or very good quality of life), physical functioning was impaired (median 40 out of a 100 (100 corresponding to unimpaired functioning) and 26 out of 40 on the work and social adjustment scale (40 corresponding to poor functioning).

	Intervention group (n=93)	**Control group (n=93)**
Demographics		
Age in years, mean (SD)	48 (15)	49 (15)
Sex, % female	73%	70%
Not in work	78%	70%
For non-medical reasons	20%	16%
On health-related benefits < 2 years	21%	16%
On health-related benefits > 2 years	37%	38%
Referring center (% academic hospital)	55%	55%
Symptoms		
Duration of motor symptoms in months, mean (SD)	70 (108)	66 (105)
Severity all presenting motor symptoms (CPS) (% moderately severe/severe/very severe)	81%	82%
Main motor symptom according to the referring neurologist		
Tremor	18%	15%
Myoclonus	23%	26%
Dystonia	14%	11%
Paresis	13%	18%
Gait disorder	15%	18%
Mixed/unclear	17%	12%
Pain (RAND36) median (IQR)	45 (55)	57 (47)
Fatigue (CIS severity), median (IQR)	44 (16)	46 (17)
Depression (PHQ9), median (IQR)	9 (9)	7 (7)
Anxiety (GAD7), median (IQR)	6 (10)	5 (9)
Health Anxiety (WI), median (IQR)	3 (2)	3 (2)
Self-rated health, quality of life and functioning		
Self-rated health (CGI),% moderately bad and bad and very bad	43%	39%
Quality of life (WHO-QoL), % good and very good	32%	29%
Physical functioning (RAND36) median (IQR)	40 (45)	40 (50)
Work and social adjustment (WSAS), median (IQR)	26 (18)	26 (15)
Illness beliefs and satisfaction with care (% agree and strongly agree)		
I am confident that the diagnosis functional disorder is correct.	63%	61%
I am afraid that something (e.g a possible serious diagnosis) has been missed when making the diagnosis.	15%	17%
My symptoms are caused by stress/worry or psychiatric problems in the past	19%	25%
Functional movement disorders are disorders of the nervous system	56%	51%
My disorder is a mystery to me (IPQ)	56%	48%

What I do determines the outcome of my disorder (IPQ)	54%	63%
My disorder is rather permanent then temporary (IPQ)	51%	48%
I think physiotherapy will improve my symptoms	37%	33%
I think psychotherapy will improve my symptoms	19%	17%
I have confidence in my neurologist	65%	58%
My neurologist and I agree on the nature of my symptoms	61%	52%
I would recommend the care I received to other patients	27%	31%
Communication with doctors (PSQ)	3 (1)	3 (1)
Interpersonal relation doctors (PSQ)	4 (1)	4 (1)
Technical quality of doctors (PSQ)	3 (1)	3 (1)

Table 1. Baseline data by treatment arm. Higher scores represent bad outcome in: CGI, CPS, CIS, PHQ, GAD, WI, WSAS, higher scores represent good outcome in: RAND36. CPS= change in presenting symptoms scale, RAND36 = Dutch equivalent of SF36 Health Related quality of life, PHQ-9=Patient Health questionnaire, GAD-7 = Generalized Anxiety Disorder Questionnaire health anxiety WI=Whitely Index, WHO-QOL = a single question from the WHO Quality of Life (Group, 1998), WSAS = Work and Social Adjustment Scale, IPQ = Illness Perception Questionnaire (IPQ) (see table 1 and 2) and the PSQ = patient satisfaction questionnaire. All statements on illness and satisfaction agreement were measured on 5-point Likert scale (1=totally disagree, 2 =disagree, 3 = agree nor disagree, 4 = agree, 5 = totally agree), percentages are displayed for readability, statistics were performed on the whole scale.

OUTCOME

Main outcome

At three months, 44% (n=31) of patients in the intervention group reported improvement of their general health ('minimally', 'much' or 'very much' improved), compared to 40% (n=26) of the controls on the CGI, the Mann-Whitney U test on the whole scale provided U=2247, p=0.899. At six months, 42% (n=35) of patients in the intervention group reported to have improved, compared to 43% (n=34) in the control group (U=3087, p=.435). Figure 2 shows the CGI scale for both groups.

The sensitivity analysis with imputed data did not result in a different main outcome.

To investigate potential harm, the number of patients with worse general health on the CGI was compared between groups. At three months 20 (29%) patients in the intervention group reported worse general health, compared to 18 controls (28%) (U=2255, p=0.910). At six months 30 patients in the intervention group (36%) had worse outcome, compared to 21 controls (27%) (U=3015, p=0.210).

The per protocol analysis (where patients that never logged on to the website were excluded from the intervention group) did not show a significant difference between groups either (see supplementary table 1).

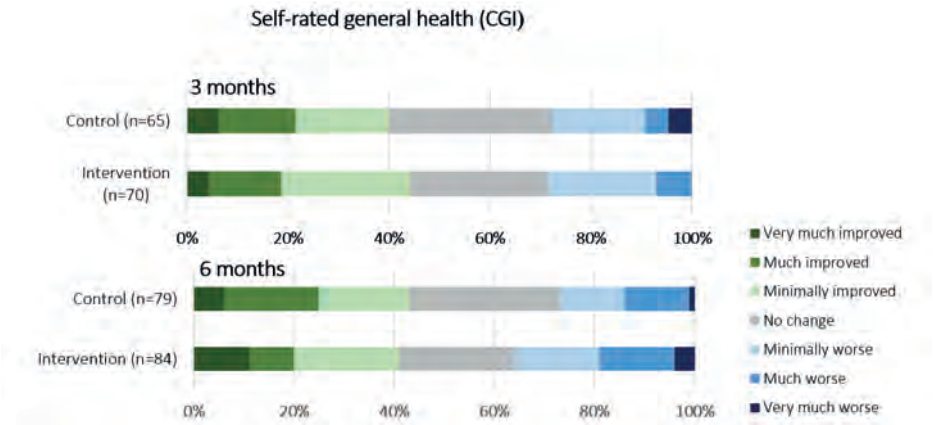


Figure 3. Main outcome, change in self-rated general health at three and six months compared to baseline in both groups.

Secondary outcomes

There were no differences between groups on any of the outcome measures at three and six months follow-up, using a cut off for statistical significance of $p<0.01$.

Symptom severity of all functional motor symptoms improved in less than half of the patients (between 40 and 44%) at 3 and 6 months in both groups compared to baseline. Depression scores were significantly higher in the intervention group than in the control group at baseline, while at three and six months this equalized. Anxiety and health anxiety remained stable over time in both groups, as well as pain, fatigue, physical functioning, quality of life and work and social adjustment.

There were no significant differences between groups on the illness perception questions. Agreement with the statement 'I am confident that the diagnosis of a functional disorder is correct' was higher in the intervention group (62%) than in the control group (47%) at three months, but this did not reach significance ($p=0.014$). Less than half of the patients (36% of controls vs 41% of patients in the intervention group at 3 months, $p=0.089$ and 26% vs 41% at 6 months, $p=0.052$) believed physiotherapy would improve their symptoms, and an even smaller number believed psychotherapy would improve their symptoms (20% of controls, 27% of patients in the intervention group, $p=0.101$ at 3 months, 19% vs 20%,$p=0.963$ at 6 months), neither changed significantly over time. Overall satisfaction with their clinical care (i.e. care other than the website) increased slightly over time (at baseline 29% of patients would recommend their clinical care to others, at 3 months follow-up 36% of controls vs 54% of patients in the intervention group, at 6 months 38% vs 47%).

There were no statistically different outcomes from the per protocol analysis (supplementary table 1).

Other websites and other treatments

During the study, four patients in the intervention group and three patients in the control group reported to have read information on the English website neurosymptoms.org. 12% of patients in the intervention group and 20% in the control group (Chi squared 2.5, p=0.111) visited one or more other related websites.

In the first three months, 69% of the patients in the intervention group received physiotherapy and 68% in the control group. Respectively 33% and 37% received some form of psychotherapy. 19% of the intervention group and 15% of controls reported to have received no therapy at all. Between three and six months, 49% of the intervention group and 50% of controls received physiotherapy, 23% and 26% respectively received psychotherapy and 17% / 18% respectively reported to have received no therapy.

Hospital admissions

Twelve patients in the intervention group (14%) were admitted to the hospital during the six months follow-up period; related to motor FND (n=6) unrelated (n=4) missing information (n=2). Twelve controls (15%) were admitted to the hospital during the 6 months follow-up period; related to motor FND (n=7), unrelated (n=4), missing information (n=1).

Post-hoc correlations

Correlation between baseline variables and outcom

Duration of symptoms of more than 6 months at baseline (mean duration at baseline was 5.7 years) was associated with bad general health outcome at six months in a univariable logistic regression model, odds ratio (OR): 2.80 (1.45-5.42) p=0.002. 59% of patients with short duration improved, compared to 37% with long (>6 months) duration of symptoms. This relationship was stronger in the intervention group (*interaction group x duration of symptoms*, OR 1.84 (1.05-3.20), p=0.033), although not significantly. Outcome was worse in men (28% of patients were man), OR 2.94 (1.58-5.48) p=0.001, which was not significantly different between groups. A number of variables were not significantly associated with outcome in the entire cohort, nor in the groups separately: The referring centre (55% of patients were referred from an academic center) (OR: 1.49 (0.86– 2.60), p=0.158), older age at onset (OR 1.02 (1.00 – 1.04), p=.026), 'I am confident that the diagnosis functional disorder is correct' (62% agreed), OR 1.14 (0.84-1.55), p=0.405. 'My disorder is a mystery to me' (52% agreed) OR 1.07 (0.86-1.33), p=0.533. 'What I do determines the outcome of my disorder' (58% agreed) OR 0.98 (0.77-1.24), p=0.877.

	3 months					6 months				
	Intervention		Control			Intervention		Control		
	N		N		Group comparison	N		N		Group comparison
Self-rated health (CGI), % improved	70	44%	65	40%	U=2247 P=0.899	84	42%	79	43%	U=3087 P=0.435
Symptoms, median (IQR) / % improved										
Severity all motor symptoms % improved	70	53%	65	38%	U=2247 p=0.899	84	42%	79	44%	U=3087 p=0.435
% of totally remitted motor symptoms	70	5%	65	0%	-	84	6%	79	4%	-
Pain (RAND36)	69	55 (68)	65	57 (44)	U=2239 P=0.989	79	55 (68)	69	57 (40)	U=2563 P=0.533
Fatigue (CIS severity)	-	-	-	-	-	71	42 (20)	66	44 (23)	U=2180 P=0.674
Depression (PHQ9)	69	6 (7)	65	7 (6)	U=1756 P=0.040	79	6 (8)	69	6 (8)	U=2170 P=0.056
Anxiety (GAD7)	70	5 (9)	65	4 (8)	U=2250 P=0.912	79	5 (9)	69	5 (8)	U=2704 P=0.933
Health Anxiety (WI)	-	-	-	-	-	74	2 (4)	68	2 (2)	U=2419 P=0.689
Quality of life and functioning, median (IQR)										
Quality of life (WHO-QoL) % good, very good	70	41%	65	29%	U=2232 P=0.838	84	40%	79	42%	U=3290 P=0.863
Physical functioning (RAND36)	70	50 (61)	65	40 (53)	U=2274 P=0.996	79	40 (65)	69	45 (58)	U=2407 P=0.217
Work and social adjustment (WSAS)	70	21 (19)	65	25 (14)	U=2170 P=0.643	81	25 (18)	69	24 (18)	U=2757 P=0.887
Illness beliefs and satisfaction with care, % agree / strongly agree										
I am confident that the diagnosis functional disorder is correct.	73	62%	66	47%	U=1863 P=0.014	76	58%	70	56%	U=2346 P=0.193

I am afraid that something (eg possible serious diagnosis) has been missed	72	18%	66	17%	U=2104 P=0.220	79	20%	69	19%	U=2347 P=0.718
Symptoms are caused by stress/worry or psychiatric problems in the past	73	19%	66	23%	U=2277 P=.548	76	21%	69	20%	U=2502 P=.610
Functional movement disorders are disorders of the nervous system	73	60%	66	52%	U=2329 P=.719	76	39%	69	48%	U=2561 P=.801
My disorder is a mystery to me (IPQ)	73	41%	66	47%	U=2112 P=0.246	76	34%	69	46%	U=2286 P=0.211
What I do determines the outcome of my disorder (IPQ)	73	59%	66	65%	U=2047 P=0.116	76	45%	69	57%	U=2319 P=0.217
My disorder is rather permanent then temporary (IPQ)	73	48%	66	55%	U=2197 P=0.344	77	58%	69	65%	U=2448 P=0.389
Exercise worsens my symptoms	73	51%	66	56%	U=1989 P=0.072	76	49%	69	64%	U=2161 P=0.035
I think physiotherapy will improve my symptoms	73	41%	66	36%	U=2020 P=0.089	76	41%	69	26%	U=2148 P=0.052
I think psychotherapy will improve my symptoms	73	27%	66	20%	U=2004 P=0.101	76	20%	69	19%	U=2576 P=0.962
I would recommend the care I received	76	54%	66	36%	U=2112 P=0.095	81	47%	69	38%	U=2725 P=0.659

Table 2. Outcome measures at 3 and 6 months in the intervention and control group (intention to treat). Absolute numbers at follow-up are displayed, mann-Whitney U tests on the difference between follow-up and baseline. Higher scores represent bad outcome in: CGI, CPS, CIS, PHQ, GAD, WI, WSAS, higher scores represent good outcome in: RAND36. CPS= change in presenting symptoms scale, RAND36 = Dutch equivalent of SF36 Health Related quality of life, PHQ-9=Patient Health questionnaire, GAD-7 = Generalized Anxiety Disorder Questionnaire health anxiety WI=Whitely Index, WHO-QOL = a single question from the WHO Quality of Life (Group, 1998), WSAS = Work and Social Adjustment Scale, IPQ = Illness Perception Questionnaire (IPQ), PSQ = patient satisfaction questionnaire. For all statements on illness and satisfaction agreement was measured on 5-point Likert scale (1=totally disagree, 2 =disagree, 3 = agree nor disagree, 4 = agree, 5 = totally agree), percentages are displayed for readability, statistics were performed on the whole scale.

Correlation between change in illness perceptions and outcome

The effect of *change* in understanding the diagnosis (measured on a change on three illness perception questions) on the main outcome at six months (general health on the CGI) was investigated by univariable ordinal regression. An increase in agreement from baseline to six months with 'I am confident that the diagnosis functional disorder is correct', provided an odds ratio of 1.43 (1.12-1.83), p=0.004 with good general health (CGI) at six months in the entire cohort. When the randomisation group was added as an interaction term, the odds ratio was 1.42 (1.01-2.00), p=0.044, indicating there was a trend towards a bigger effect in the intervention group. A decrease in agreement with 'My disorder is a mystery to me' (odds ratio 1.30 (1.02 – 1.63), p=0.033), and an increase in agreement with 'What I do determines the outcome of my disorder' (odds ratio: 1.13 (0.93– 1.36), p=0.234), were not significantly associated with outcome.

Evaluation of the education and self-help website

63 patients in the intervention group (74% of the 85 that viewed the website at least once), filled out the evaluation. 86% of patients reported they would recommend the website to other patients, 68% of patients found the website very useful, and 67% performed the exercises provided on the website at some point during the 6 months follow-up.

A smaller number of patients answered more detailed questions evaluating the website (n=55). 78% agreed with the explanation of their symptoms that was provided on the website, 89% found the information on the website was easy to understand, 22% perceived difficulty in taking in the information, 49% agreed the information on the website matched the explanation given by the neurologist they had seen for their symptoms, and 75% reported they would want to keep on using the website in the future. Of them, 9% reported they felt angry or misunderstood (for divergent and sometimes multiple) reasons: the website was patronising (n=2), too negative (n=1), a specific symptom the patient suffered from was not mentioned (n=1), the website created a stronger focus on the symptoms, which was unhelpful (n=1), physical exercises made the symptoms worse (n=1), there was a discrepancy between the opinion of health care providers in reality and the information on the website (n=1).

In additional comments, patients mentioned they experienced health care providers seemed to lack knowledge on functional neurological disorders (n=10), which either impeded treatment generally, or it made the website less helpful because of the lack of connection with their experience of healthcare (some felt this was highly

frustrating). Others remarked the website was actually helpful to educate their health care providers and/or explain the disorder to relatives and friends. Several patients (n=10) mentioned they felt heard after reading the website and felt it validated their experiences, or they were relieved to see other patients had very similar symptoms and impairments. Three patients asked for an overview of health care providers with experience in this field or a patient-forum (n=3).

DISCUSSION

In this randomised controlled trial there was no difference in self-rated general health on the clinical global improvement scale at three or six months between motor FND patients who were directed towards an education and self-help website in addition to usual care and patients who received only usual care. Nor were there significant differences on the secondary outcomes (severity of motor symptoms, other physical and psychiatric symptoms, physical functioning, quality of life, work and social adjustment, or illness beliefs (including beliefs of the effect of physiotherapy/psychotherapy and satisfaction with care)). Patient satisfaction with the website was high. The per protocol analysis results were similar to the primary intention to treat analysis.

Our results suggest non-guided online self-help is not effective as a sole addition to usual care for motor FND. There are no studies of unguided self-help and education for motor FND to compare our data with. A meta-analysis of self-help in the broader group of functional syndromes (chronic pain, chronic fatigue and irritable bowel syndrome), showed improvement of quality of life and/or symptom reduction of both guided and unguided self-help, although outcome measures were heterogeneous and there were only five unguided studies [12]. A recent meta-analysis of treatment modalities in depression, also showed unguided self-help therapy was not more effective than care as usual, while guided self-help was [20]. Our findings support patient group concerns, for example expressed by individual patients and patient organisations [28] that an unguided self-help website should not be regarded as all that is needed to manage motor FND. Motor symptoms improved in roughly two out of five patients spontaneously after diagnosis. This suggests that neurologists should follow FND patients up after diagnosis to monitor early improvement and to direct the remaining three out of five patients to further treatment, and not rely on the provision of information alone as treatment.

Providing patients with reliable and accessible information does not need to resolve or even improve symptoms in order to be justifiable. We showed no additional harm was done by the intervention (bad outcome and hospitalisations were as frequent in both arms). It is notable that the intervention was well received. 78% agreed with the explanation of the disorder on the study website, and 86% of patients reported they would recommend the website to other patients. Although it did not lead to demonstrable improvements in health status, 68% of patients reported they found the website very helpful. The website appeared to provide a sense of 'acceptance' and a feeling of being 'heard', which is a worthwhile goal in its own right.

Explanation and education remain, in our view, an essential element of stepped care for motor FND. Improved confidence that the diagnosis was correct correlated with improvement in health across the whole cohort, and to a greater extent in the intervention group, although the latter did not reach the predetermined threshold ($p<0.01$) for significance. Nonetheless this suggests the right direction of travel in terms of improving understanding. Treatment studies of motor FND using a comparable educational model, either as a guided self-help intervention [11], or combined with physical and cognitive behavioural interventions in inpatient [21–23] or outpatient [24, 25] settings, have shown favourable outcomes. In practice though, patients often experience lack of availability of expert knowledge, as reflected in patients' written comments and the finding that only half (49%) of the patients agreed that the information from the website matched with the explanation of the neurologist. This is a problem recognised by physicians in the field [26] and emphasises the need for consistency between health professionals caring for the same patient.

The study had several limitations. Patients in our study had a long duration of symptoms (mean of 5.6 years), which may have negatively influenced outcomes, as we found that symptom duration correlated to worse outcome. Prognostic studies [3] in general have found that a longer duration of symptoms correlates with poorer prognosis. Early intervention seems beneficial in some conditions commonly comorbid with motor FND [27, 28].

The fact that we employed liberal inclusion criteria and advertised the study broadly (with good result: 31 centers, both academic and non-specialised, referred patients), improved generalizability. This is to date the largest RCT in any FND. Also, the overall improvement of motor symptoms in 40-44% of patients is comparable to other cohorts [29, 30]. However, selection bias most likely occurred at patient level (patients who did not believe the diagnosis were less likely to enrol), and physician

level (neurologists with an interest in FND would be more likely to refer into the study). A large number of patients (n=128) refused to take part, In addition, 17 patients never completed the baseline questionnaires and many patients only viewed the website a few times. Follow-up rates were 70 % vs 75% in the control vs intervention group at three months and 85% vs 90% at six months.

Outcomes might have been influenced because the study was not blinded, a nocebo effect in the control group could have occurred. However, this effect is likely to be small in this low-intensity study. Use of alternative websites like neurosymptoms.org was low and equal between groups. Furthermore, the study website was different to the neurosymptoms.org, in that it provided a programme of information to work through, and numerous videos and examples not available elsewhere. Our patient cohort might have been too small to capture subtle differences in secondary outcomes. The follow-up period was relatively short and therefore long-term effects, for example on compliance with or effect of further treatments might have been missed. The fact that the study was internet-based, compared to on paper, did not appear to cause problems in inclusion or follow-up in the large majority of patients.

CONCLUSION

In this first randomised controlled trial of an online education and self-help programme for motor FND, we found it was well received but it did not lead to improvements in self-rated general health on the clinical global improvement scale at three or six months. Nor did it lead to any harmful effects. Furthermore, there were no differences between groups on any secondary outcome measures.

Overall, our findings support neurologists offering supplementary self-help materials at time of diagnosis, but we caution that such materials should not be regarded as efficacious treatment in their own right.

REFERENCES

1. Espay A. The first step in the mangement of functional neurologic disorders: diagnostic debriefing. AAN Lect. 2017;:4–6.
2. Espay AJ, Goldenhar LM, Voon V, Schrag A, Burton N, Lang AE. Opinions and clinical practices related to diagnosing and managing patients with psychogenic movement disorders: An international survey of movement disorder society members. Mov Disord. 2009;24:1366–74. doi:10.1002/mds.22618.
3. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. J Neurol Neurosurg Psychiatry. 2014;85:220–6. http://www.ncbi.nlm.nih.gov/pubmed/24029543.
4. Carton S, Thompson PJ, Duncan JS. Non-epileptic seizures: patients' understanding and reaction to the diagnosis and impact on outcome. Seizure. 2003;12:287–294.
5. Silva W. Clinical Features and Prognosis of Nonepileptic Seizures in a Developing Country. Epilepsia. 2001;42:398.
6. Sharpe M, Walker J, Williams C, Stone J, Cavanagh J, Murray G, et al. Guided self-help for functional (psychogenic) symptoms. Neurology. 2011;77:564–72.
7. Mckenzie PS, Oto M, Graham CD, Duncan R. Do patients whose psychogenic non-epileptic seizures resolve , ' replace ' them with other medically unexplained symptoms ? Medically unexplained symptoms arising after a diagnosis of psychogenic non-epileptic seizures. 2011;:967–70.
8. Duncan R, Razvi S, Mulhern S. Newly presenting psychogenic nonepileptic seizures: Incidence, population characteristics, and early outcome from a prospective audit of a first seizure clinic. Epilepsy Behav. 2011;20:308–11. doi:10.1016/j.yebeh.2010.10.022.
9. Hall-Patch L, Brown R, House A, Howlett S, Kemp S, Lawton G, et al. Acceptability and effectiveness of a strategy for the communication of the diagnosis of psychogenic nonepileptic seizures. Epilepsia. 2010;51:70–8.
10. Salmon P, Peters S, Stanley I. Patients' perceptions of medical explanations for somatisation disorders: qualitative analysis. BMJ. 1999;318 February:372–6.
11. Sharpe M, Walker J, Williams C, Stone J, Cavanagh J, Murray G, et al. Guided self-help for functional (psychogenic) symptoms: A randomized controlled efficacy trial. Neurology. 2011;77:564–72.
12. Van Gils A, Schoevers RA, Bonvanie IJ, Gelauff JM, Roest AM, Rosmalen JGM. Self-help for medically unexplained symptoms: A systematic review and meta-analysis. Psychosom Med. 2016;78:728–39.
13. Edwards MJ, Adams R a., Brown H, Pareés I, Friston KJ. A Bayesian account of "hysteria." Brain. 2012;135:3495–512.
14. Stone J. Functional neurological disorders: The neurological assessment as treatment. Pract Neurol. 2016;16:7–17. doi:10.1136/practneurol-2015-001241.
15. Stone J, Carson A, Hallett M. Chapter 44 – Explanation as treatment for functional neurologic disorders. 1st edition. Elsevier B.V.; 2016.
16. Nielsen G, Stone J, Matthews A, Brown M, Sparkes C, Farmer R, et al. Physiotherapy for functional motor disorders : a consensus recommendation. 2014;:1–7.
17. Gelauff JM, Kingma EM, Kalkman JS, Bezemer R, van Engelen BGM, Stone J, et al. Fatigue, not self-rated motor symptom severity, affects quality of life in functional motor disorders. J Neurol. 2018;265:1803–9.
18. Sharpe M, Walker J, Williams C, Stone J, Cavanagh J, Murray G, et al. Guided self-help for functional (psychogenic) symptoms A randomized controlled efficacy trial. Neurology. 2011;77:564–72.

19. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. J Neurol Neurosurg Psychiatry. 2013;:jnnp--2013.
20. Cuijpers P, Noma H, Karyotaki E, Cipriani A, Furukawa TA. Effectiveness and Acceptability of Cognitive Behavior Therapy Delivery Formats in Adults with Depression: A Network Meta-analysis. JAMA Psychiatry. 2019;76:700–7.
21. Saifee T a., Kassavetis P, Pareés I, Kojovic M, Fisher L, Morton L, et al. Inpatient treatment of functional motor symptoms: A long-term follow-up study. J Neurol. 2012;259:1958–63.
22. Jordbru AA, Smedstad LM, Klungsøyr O, Martinsen EW. Psychogenic gait disorder: a randomized controlled trial of physical rehabilitation with one-year follow-up. J Rehabil Med. 2014;46:181–7. doi:10.2340/16501977-1246.
23. McCormack R, Moriarty J, Mellers JD, Shotbolt P, Pastena R, Landes N, et al. Specialist inpatient treatment for severe motor conversion disorder: a retrospective comparative study. J Neurol Neurosurg Psychiatry. 2014;85:895–900. doi:10.1136/jnnp-2013-305716.
24. Nielsen G, Buszewicz M, Stevenson F, Hunter R, Holt K, Dudziec M, et al. Randomised feasibility study of physiotherapy for patients with functional motor symptoms. J Neurol Neurosurg Psychiatry. 2017;88:484–90. doi:10.1136/jnnp-2016-314408.
25. Czarnecki K, Thompson JM, Seime R, Geda YE, Duffy JR, Ahlskog JE. Functional movement disorders: Successful treatment with a physical therapy rehabilitation protocol. Park Relat Disord. 2012;18:247–51. doi:10.1016/j.parkreldis.2011.10.011.
26. Espay AJ, Goldenhar LM, Voon V, Schrag A, Burton N, Lang AE. Opinions and clinical practices related to diagnosing and managing patients with psychogenic movement disorders: An international survey of movement disorder society members. Mov Disord. 2009;24:1366–74.
27. Brison R, Hartling L, Dostaler S, Leger A, Rowe B, Stiell I, et al. A randomized controlled trial of an educational intervention to prevent the chronic pain of whiplash associated disorders following rear-end motor vehicle collisions. Spine (Phila Pa 1976). 2005;30:1799–807.
28. Oliveira A. A Psycho-Educational Video Used in the Emergency Department Provides Effective Treatment for Whiplash Injuries. Spine (03622436). 2006;31:1652–7. http://10.0.4.73/01.brs.0000224172.45828.e3%0Ahttp://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=21461926&site=ehost-live.
29. Carson AJ, Best S, Postma K, Stone J, Warlow C, Sharpe M. The outcome of neurology outpatients with medically unexplained symptoms: a prospective cohort study. J Neurol Neurosurg Psychiatry. 2003;74:897.
30. Gelauff JM, Carson A, Ludwig L, Tijssen MAJ, Stone J. The prognosis of functional limb weakness: a 14-year case-control study. Brain. 2019;0:1–12.

Acknowledgements

We are grateful for all neurologists who referred patients to this study from the 31 centres in the Netherlands.

Funding

This study was funded by Stichting MIND (previously: Fonds Psychische Gezondheid), with an unrestricted grant. JS is supported by an NHS Scotland NRS Clinical Fellowship. The pilot study that preceded this RCT, was supported by an unrestricted healthy-aging pilot-project grant from the University of Groningen. GN receives research funding from the National Institute for Health Research (NIHR).

Conflicts of interest

JS has run a self-help website for functional neurological disorder, www.neurosymptoms.org since 2009 which is free and carries no advertising.

Supplementary table per protocol:

	3 months					6 months				
	Intervention		Controls			Intervention		Controls		
	N		N		Group comparison	N		N		Group comparison
Self-rated health (CGI), % improved	58	45%	65	40%	U=1879 P=.975	78	42%	79	43%	U =2851 P=.412
Symptoms, median (IQR) / % improved										
Severity all motor symptoms (CPS)	63	51%	66	38%	U=1982 P=.641	79	51%	79	44%	U=3002 P=.581
% of remitted motor symptoms		6%		0%	-		6%		4%	-
Pain (RAND36)	57	45 (58)	65	57 (43)	U=1816 P=.851	73	45 (68)	69	57 (40)	U=2370 P=.543
Fatigue (CIS severity)		NA		NA		66	43 (21)	65	44 (13)	U=2023 P=.574
Depression (PHQ9)	57	7 (8)	65	7 (5)	U=1517 P=.084	71	8 (9)	69	6 (8)	U=2041 P=0.088
Anxiety (GAD7)	58	6 (10)	65	4 (8)	U=1863 P=.909	73	5 (9)	69	5 (8)	U=2485 P=.887
Health Anxiety (WI)		NA		NA		70	2 (3)	68	2 (2)	U=2293 P=.705
Quality of life and functioning, median (IQR) / % good										
Quality of life (WHO-QoL) % good / very good	58	67%	65	29%	U=1833 P=.776	78	37%	79	41%	U=2909 P=.531
Physical functioning (RAND36)	58	48 (67)	65	40 (52)	U=1870 P=.937	73	40 (65)	69	45 (58)	U=2477 P=.865
Work and social adjustment (WSAS)	58	22 (18)	65	25 (13)	U=1779 P=.588	75	26 (19)	69	24 (18)	U=2380 P=.405
Illness beliefs and satisfaction with care, median (IQR)										
I am confident that the diagnosis functional disorder is correct.	59	61%	66	47%	U=1487 P=.014	70	58%	70	56%	U=2114 P=.138

I am afraid that something (eg possible serious diagnosis) has been missed	58	14%	66	17%	U=1667 P=.189	70	23%	69	19%	U=2214 P=.373
Symptoms are caused by stress/worry or psychiatric problems in the past	59	19%	66	23%	U =1883 P =.731	70	20%	69	20%	U=2234 P=.409
Functional movement disorders are disorders of the nervous system	59	59%	66	52%	U=1860 P=.649	70	59%	69	48%	U=2396 P=.933
My disorder is a mystery to me (IPQ)	58	40%	66	47%	U=1603 P=.108	69	31%	69	46%	U=2042 P=.134
What I do determines the outcome of my disorder (IPQ)	59	63%	66	65%	U=1759 P=.335	70	46%	69	57%	U=2152 P=.252
My disorder is rather permanent then temporary (IPQ)	59	46%	66	55%	U=1644 P=.111	71	59%	69	65%	U=2225 P=.323
Exercise worsens my symptoms	59	51%	66	59%	U=1579 P=.065	70	55%	71	62%	U=2003 P=.044
I think physiotherapy will improve my symptoms	59	44%	66	36%	U=1491 P=.019	70	41%	69	26%	U=1881 P=0.019
I think psychotherapy will improve my symptoms	59	29%	66	20%	U=1592 P=.069	69	21%	69	19%	U=2373 P=.972
I would recommend the care I received	63	62%	66	36%	U=1866 P=.301	74	48%	71	37%	U=2566 P=.802

Supplementary Table 1. Data is displayed at follow-up, tests are performed on the change between follow-up and baseline.

Summary and general discussion

In the introduction we drafted how developments within the field of FMD in the last decade were the basis for the outline of this thesis. From these developments, we postulated new questions concerning the topics of the pathophysiology, prognosis and treatment of FMD. Below, we summarize the most important findings from each chapter within these three themes. This is followed by a more in depth discussion on a number of topics originating from our results: lumping and splitting, sense of agency and the measurement of outcome in FMD. Furthermore, we will discuss the implications of these findings for future studies and for clinical practice. We will finish with a number of personal reflections that arose during the work on this thesis.

RESULTS OF THE THESIS

Part 1. Pathophysiology

To better understand FMD, both clinical observation and experimental studies are needed. Clinical observational studies give insights in underlying mechanisms and provide us with new hypotheses. Experiments can challenge these hypotheses and unravel the specific mechanisms underlying FMD.

Clinical aspects

The clinical picture of FMD is heterogenous in terms of symptoms, risk factors, triggers and co-morbidity. Even within the same patient the type, severity and localization of FMD symptoms can change over time. Although not often systematically investigated, many studies have shown large numbers of additional functional and psychiatric symptoms in patients with FMD. There is a growing realization of the importance of non-motor symptoms in FMD.

Chapter 1 described a comparison between patients with different functional motor symptoms. The main motor symptom was categorised by the neurologist, resulting in the following groups: tremor, myoclonus, dystonia, paresis and gait disorder. We investigated demographics, mode of onset, non-motor symptoms, quality of life and functioning and self-rated additional motor symptoms. There were no differences between groups, except that impairment of physical functioning was worse in patients with functional paresis or gait disorder as the dominant motor symptom.

In **chapter 2** we compared fatigue between the patients included in the SHIFT trial (chapter 10) and a group of patients with neuromuscular disorders [1]. We used the checklist individual strength (CIS) fatigue questionnaire, which contains four

subdomains of fatigue. Patients with FMD had higher scores compared to the group of neuromuscular disorders on all these subdomains (fatigue severity, motivation, concentration, physical activity). Severe fatigue (>34 on the fatigue severity subdomain) was present in 78% of patients with FMD, compared to 53% of patients with neuromuscular disorders ($p < 0.001$). We found fatigue, but not symptom severity, influenced self-rated general health and quality of life in FMD. We found correlations between fatigue and motor symptom severity, depression and anxiety. Therefore fatigue is most likely both a co-morbid symptom as a consequence of (chronic) multimorbidity.

In **chapter 3** we found that fatigue, depression and anxiety were as high in functional myoclonus as in ('organic') cortical myoclonus. Pain was the only non-motor symptom that was worse in functional myoclonus. Additionally, we found that functional myoclonus severity was correlated to anxiety and depression, while this was not the case in the cortical myoclonus group. Despite the limitations of a small sample size (functional myoclonus n=16, cortical myoclonus n=23) in a tertiary clinic, we concluded that both functional and cortical myoclonus patients suffer from comorbid psychiatry to the same extent. This contradicts often held beliefs that functional movement disorders would be more strongly associated with psychiatric comorbidity. We found that the relationship between anxiety and depression and functional myoclonus is most likely bidirectional.

Experimental aspects

In the experimental studies that we performed, the concepts of sense of agency, attention to the self and perception of body scheme were central.

In **chapter 4** we describe an experiment in which we aimed to elicit a decrease in the sense of agency when performing a motor task (pressing a button), by manipulating the feedback patients received. This manipulation consisted of a variable delay in time between button press and the sound resulting from that. Subjects were asked if they felt they were the cause of the sound that followed a button press, or not. This was performed in the same patients and healthy controls that underwent fMRI scanning in chapter 5 and 6. We did not find differences between groups. We concluded that the chosen paradigm most likely does not resemble the exact element of sense of agency that is disturbed in FMD. Explicit sense of agency, which is considered to be conceptually different from implicit sense of agency [2], might be less affected than implicit sense of agency in FMD.

In chapter 5 and 6 we performed two different fMRI paradigms, in a group of 17 patients with functional tremor and/or jerky movements, compared to 17 healthy controls.

In **chapter 5** we performed an action selection task fMRI study to investigate the neural correlates of perception of body scheme and sense of agency in FMD. In this action selection task, subjects were alternatingly choosing or instructed to use either a finger of a button, resulting in two axes of comparison: free versus fixed and button versus finger selection. We confirmed findings in healthy controls of predominantly prefrontal and parietal activations in free versus fixed conditions; the opposite contrast showed the extra striate visual cortex and activation along the dorsal intraparietal sulcus. In finger versus button selection, we found activations of the occipital and anterior parietal cortices, including the postcentral sulcus. This reaffirmed the notion that voluntary action resides in both prefrontal areas and the parietal cortex [4, 5]. In FMD compared to healthy controls, we found reduced activation of the left primary motor cortex in the conjunction of all motor conditions, attributed to disrupted explicit motor control in FMD. This finding fits with the notion that patients are experiencing difficulties 'accessing' normal initiation of movement, as often vocalized in clinical practice. The left insula showed reduced activity in free finger selection and activity of the insula in this contrast was also correlated to symptom severity in patients. This confirmed our hypothesis of alterations in sense of agency and perception of body scheme in FMD, and confirmed earlier studies showing involvement of the insula [6–8].

In **chapter 6** we performed an exploratory resting state study, investigating brain networks using a data-driven approach: independent component analysis. We found altered regional brain activity in the component consisting of the (pre)cuneus and posterior cingulate cortex (PCC), consisting of decreased power of lower-range frequency fluctuations and increased power of upper-range frequency fluctuations. Both the (pre)cuneus and PCC network, as well as the cuneus and inferior parietal lobe are known to be involved in attention shifting and sense of agency. Although the time course fluctuations have been found to correlate with altered brain activity and with other measures of functional connectivity[3], they are relatively unexplored. This impedes too strong conclusions concerning these time course fluctuations. Our findings confirm the role of brain regions implicated in sense of agency and altered attentional processes in FMD.

The most noticeable aspect of the combined findings of chapter 5 and 6 is the scarcity of differences between FMD and healthy controls within the resting state whole brain approach in chapter 6, while more outspoken differences were found when testing the specific hypothesis in chapter 5. This indicates differences in brain activity between groups might be subtle and specific.

Part 1 Implications

Based on our studies and the literature, we concluded that similar to patients with non-functional movement disorders, non-motor symptoms like pain and fatigue and psychiatric co-morbidity, should not be underestimated in FMD and need more attention in history taking, treatment studies and treatment strategies.

The findings from our fMRI studies confirm the theories of altered direct motor control, abnormal sense of agency and perception of body scheme. Amongst others, this underpins the role of focusing on relearning normal, automatic movements to 'retrain the brain' in the treatment of FMD.

Part 2. Prognosis

In order to determine the prognosis of FMD, we performed a systematic review (**chapter 7**) and the largest and longest follow-up study in FMD (limb weakness) (**chapter 8**).

The systematic review of 24 mostly retrospective studies that were heterogeneous in terms of size, follow-up duration and clinical setting showed a rough mean percentage of patients that were the same or worse at follow-up for all studies of 39%, (range 10% - 90%). We also found that poor symptom outcome goes hand-in-hand with a loss of quality of life and impairment. That indicates a generally unfavorable prognosis of FMD.

Chapter 8 is a follow-up study of a large cohort of patients with functional weakness, a control group of patients with neurological disease causing limb weakness, and a healthy control group [9]. Symptom outcome in our study was largely the same as in the systematic review: 20% of patients had totally remitted functional motor symptoms at follow-up. Compared to the control group of neurological disease, functional weakness did improve more often over the 14 year follow-up period. However, most secondary measures (like general health, physical functioning and work) showed FMD patients and neurological controls had comparably bad outcomes, which were significantly worse than in the healthy control group.

Misdiagnosis was very rare (1 patient in the FMD group and 1 neurological control were misdiagnosed), which confirms a literature overview [10], and a large prognostic study in FND [11].

Death rate in the functional weakness group was higher than in the healthy population, but no deaths were linked to the initial functional symptoms. Explanations of this increased death rate should be interpreted cautiously, because of the small group (n=11 deaths in the FMD group). Still we found the higher death rate in FMD is most likely due to the negative biopsychosocial side effects of having a chronic illness.

Prognostic factors were difficult to determine in both studies. From the systematic review, short duration of symptoms, early diagnosis and high satisfaction with care predicted positive outcome. Sex had no effect. Delayed diagnosis and personality disorder were negatively correlated with outcome. Prognostic factors that varied between studies included age, comorbid anxiety and depression, intelligence, educational status, marital status and pending litigation. In our follow-up study there were only univariable baseline predictors for weakness outcome: somatization disorder, general health, pain, and total symptoms.

The most important limitation from both studies is that the majority of patients had a long duration of symptoms prior to inclusion, while this is correlated with worse outcome. The data might therefore not be representative of acute functional motor symptoms. For chronic FMD prognosis seems unfavourable, especially in a tertiary setting, while misdiagnosis is rare and prognosis remains difficult to predict on an individual level.

Part 2. Implications

The follow-up data from the systematic review and prognostic study can add to a realistic explanation of the natural history of FMD to patients. It endorses FMD is a potentially reversible disorder. However, it is important to realize that FMD does not have a benign course when left untreated in a large number of patients. Our data urge physicians to take FMD seriously. It also seems advisable to start treatment early (long duration of symptoms was the strongest predictor of poor prognosis). Also, the data lend urgency for treatment studies.

Part 3. Treatment

Well conducted treatment studies in FMD are rare. In **chapter 9** we reviewed the literature on treatment for FMD. Studies with the aim to explain the diagnosis and retrain normal movement, sometimes combined with psychological treatments in a multidisciplinary setting, have been found to improve symptoms and general health outcomes. However, evidence on psychological treatments is lacking and only a small number of studies investigated multidisciplinary treatments. Although a stepped care approach is highly recommended, this is merely a utopia in clinical practice, where treatment options are very scarce. Fortunately, since the beginning of this thesis, promising results have been published. After the publication of our review, a feasibility trial into physiotherapy for FMD was published, with good results, confirming the theory that retraining automatic movements using education and distraction techniques can be beneficial [12].

In our own randomized controlled trial, in **chapter 10**, we studied the effect of an online education and self-help website added to usual care, and compared it to usual care only. The content of the website matched the theoretical framework we describe in the introduction. We randomized 186 patients to usual care with or without website access, and found no difference on the main outcome, self-rated health on the Clinical Global Improvement scale at three and six months follow-up between groups. There were no significant differences on secondary outcome measures either. However, patient satisfaction with the online intervention was high. In the entire cohort, we found a significant association between a change in confidence in the disorder and FMD outcome, which underlines the importance of education as part of treatment. Selection bias most likely occurred, because a large number of patients refused to take part and the majority of patients had long duration of symptoms. Still this is to date the largest randomized cohort study within the field of FMD, which adds important findings to the literature.

Part 3 Implications

Within FMD, evidence based treatments are scarce, but an increasing number of studies provide promising new insights. Our findings caution that self-help materials should not be regarded as the sole treatment approach.

FURTHER CONSIDERATIONS

Lumping or splitting

In part 1, we have studied the role of non-motor features in FMD. We aimed to determine their importance, but we also compared patients with different main motor symptoms, studying a possible link between certain motor and non-motor symptoms. This touches upon the long-lasting discussion on lumping or splitting the different FND syndromes [13–15]. Whether FND syndromes should be lumped together and considered one disorder, or should be considered separate disease entities is a matter of debate. As they are often defined based on the symptoms and linked to their 'organic' counterpart ('non-epileptic attacks' for example), they end up in different health services. At the same time the underlying mechanisms of these syndromes share many similarities and they are all considered to be 'functional' in nature.

The argumentation to consider all functional syndromes as a single entity was best articulated by Wessely et al in 1999 [15]. The authors noted a large overlap between different functional syndromes making discrimination between phenotypes difficult. Secondly, they argue that patients share many characteristics like sex ratios, comorbid emotional disorders and etiological factors. Thirdly, they observed a comparable response to similar treatments across studies. In neurological functional disorders, a review paper comparing non-epileptic attacks and FMD concluded that similarities exceed the differences [13], while another review concluded the opposite, based on differences in non-symptom characteristics and mode of onset [14]. A recent paper also detected differences in personality traits and psychopathology between non-epileptic attacks and FMDs [16]. Patients with non-epileptic attacks had higher levels of neuroticism and depressive and anxiety symptoms, overall psychopathology, a greater history of sexual abuse and alexithymia and more dissociative symptoms. FMD patients had higher scores of conscientiousness.

Our results showed indications of large overlap in motor symptoms between groups: The majority of patients reported to have more than one motor symptom, and there was a significant number of patients (12%) that could not be classified into one main motor group by the neurologist because these patients had several equally impairing motor symptoms. Also, similarities in signs and symptoms between groups contributed to the hypothesis of a shared underlying mechanism of functional motor disorders. Our study does not resolve the lumping versus splitting debate. However, we did not find evidence for large differences in non-motor features or

in level of impairment between the different motor symptom groups. This means that stratifying FMD is not specifically helpful when measuring outcome or when randomizing patients in treatment studies (as we did in chapter 10).

In fact, the value of studying co-morbidity in FMD is debatable. One could argue, like we did with regard to the symptom of fatigue, that the different symptoms partly share a pathophysiological mechanism, and are therefore considered part of FND itself. However, since many of the non-motor co-morbidities that we studied are highly prevalent in other (non-functional) movement disorders as well, they could be non-specific consequences of having a neurological disorder. Also, the symptoms themselves might have limited discriminating value: almost all patients with FND report a large number of varying symptoms. That could implicate they are more likely to perceive physical symptoms in general, without an underlying reason for each symptom individually.

Naturally, it remains important to take note of all symptoms a patient experiences. Whether the treatment should be focused on shared factors between patients (for example in the underlying pathophysiology) or tailored to the symptoms is not clarified yet and was not the focus of the studies in this thesis. However, it seems reasonable that there will remain the need for symptom-based treatments, like in other movement disorders. Because of the large overlap, it is desirable to adapt a holistic view and aim (multidisciplinary) treatment at all symptoms patients experience, while health services are often not equipped to offer that.

Sense of agency

In the leading explanatory theory on FMD, abnormal sense of agency and dysfunctional attentional processes play a key role. We performed two fMRI studies, the findings of both studies were compatible. The identified brain regions together form a network that is associated with sense of agency. This network has previously been described as consisting of: the lateral temporo-parietal cortex, medial frontal cortex, the dorsolateral prefrontal area, frontal operculum/insula regions and posterior midline structures, mainly the precuneus and posterior cingulate cortex [17]. Our key findings of involvement of the insula, parietal operculum and premotor cortex from the action selection paradigm (chapter 5) and the posterior midline structures (pre)cuneus and PCC, from the resting state data (chapter 6), match that network exactly. The data was derived from the same population, which makes this link stronger. Although studies have shown the involvement of many different brain areas in FMD, there is a growing body of evidence towards areas associated with

willed motor action and sense of agency. Imaging studies associated a number of brain regions with FMD, mainly comprising the insula, prefrontal regions and the parietal cortex, including the temporoparietal junction, as summarized in a recent meta-analysis and found in recent task-paradigms and resting state fMRI [6, 8]. These regions are strongly associated with willed action and sense of agency. Our data confirm that.

Additionally, our studies provided a link between the concepts of sense of agency and attentional processes, partly due to altered self-attribution to externally cued movements. This link can be explained by the phenomenon that enhanced attention to a motor task has a seemingly contradictory effect of reducing the feeling of being in control over that movement, thus reducing sense of agency. Attention and enhanced perceived effort (when movements are less *automatic*) could be partly overlapping concepts in that respect. This is shown in physiological studies in which movement control is impeded by enhanced attention [18].

Resting state findings of Maurer et al [7] showed decreased functional connectivity between the right TPJ and the right sensorimotor cortex, cerebellar vermis, bilateral supplementary motor area (SMA), and right insula in FMD compared to healthy controls. They suggest reduced sense of agency could result from the combination of distorted sensory perception and disturbed feed-forward motor control. The latter might be attributed to altered attention to movement, especially given the involvement of the SMA and insula. Thereby their data indirectly provides the same link between attentional processes and sense of agency.

fMRI studies have drawbacks impeding strong conclusions. Many different brain areas have been found to be associated with FMD in the different fMRI studies, mirroring clinical heterogeneity and revealing the influence of the large variety in study set-up [8, 19]. The study set-up is crucial in fMRI studies, and therefore conclusions should be confined to the experiment. On the one hand this is very helpful, as the experimental setting enables the opportunity to test very specific hypotheses. On the other hand there is a risk that results are interpreted within a set framework, while brain regions are known to have different functions, especially within networks. Like in our results, brain regions that we attribute to sense of agency, are not only involved in sense of agency, but also in many other functions. Within our experiment and in combination with the overall findings, it is very reasonable to interpret them as such, but it has to be noted that this is not the only possible explanation. Also, as most studies in the field are cross-sectional, it

is impossible to determine if the found abnormalities are cause or consequence of FMD and if they represent a state or a trait. Having said that, it is of interest that there is large overlap in fMRI findings between patients with dissociative non-epileptic attacks and FMD. Kruijs et al [20] performed a resting state fMRI analysis in dissociative non-epileptic attacks, and proposed a circuit based on their findings that has many resemblances with the findings from our studies. This circuit includes altered activity in the insula, cingulate gyrus, superior parietal lobe, pre- and postcentral gyri, supplementary motor cortex and the precuneus, within their network analysis. A comparative study confirms that there is overlap, when reviewing imaging studies into emotional dysregulation, dissociation and psychological trauma in the context of motor control in dissociative non-epileptic attacks and FMD [21]. Naturally, this is of interest to the above mentioned discussion on lumping or splitting functional syndromes.

Measuring treatment outcome

It is notoriously difficult to measure outcome in functional motor symptoms. Not only because their severity, symptom type and localization vary in time [22], but also because it is difficult to classify symptoms and to capture outcome that is meaningful for the patients. Here we discuss a number of considerations on measuring outcome in FMD, originating from our experiences in part 3.

The main topic of discussion is measurement by self-report, used in all studies in this thesis. In several chapters in this thesis we used patients' self-report of the motor symptoms as outcome measure. This was on the one hand a drawback to the design, but on the other hand self-report can be regarded as the most meaningful way of capturing outcome, because patients' own experience is more important than a doctors' snapshot appraisal, especially given the variable nature of the disorder. When attempting to systematically investigate (other) treatments and functional co-morbidity during follow-up in both chapter 8 and 10, we met the limitations of self-report. Because of the limited standardized treatment options available for patients, patients have difficulty verbalizing what their treatments consisted of. There is no reliable registry of this either. As for functional co-morbidity, a study investigating a questionnaire designed for this purpose concluded that it remains difficult to distinguish if symptoms were functional or not based on self-report, even if the questions asked are based on discriminating features that are widely used by physicians [23].

All studies in this thesis are limited by selection bias, which is very difficult to overcome in clinical research. Patients need to be informed and to provide consent, requiring them to at least acknowledge the diagnosis of a functional disorder, which can be a problem in FMD. Also, selection bias occurs at the level of symptom severity: patients at both sides of the spectrum (being very severely impaired or perceiving almost no impairment) are less likely to participate. In the SHIFT study, selection bias related to the referring neurologists might also apply: those with an interest in FMD were more likely to have heard of the study and could have been more eager to participate.

There are many difficult aspects of using (self-report) outcome measures in FMD. Imagine a patient with FMD who suffers from attack of myoclonus, fatigue and difficulty concentrating and who is worried about having all these symptoms, with increasingly a low mood. Should her symptoms of concentration problems and fatigue be considered part of a possible depressive disorder (considering her mood changes) or are they symptoms of the FMD? To what extent are mood changes a normal response to chronic illness or the lack of treatments available for FMD? And how can we study these different symptoms, when most questionnaires on these topics have overlapping questions? How should this patient fill out a questionnaire on physical impairment, when she only has impairing symptoms part of the time?

Scales that measure physical functioning are often more objective, but meant to be generic and therefore miss specific incapacitating symptoms (they measure walking distance, but do not include items for speaking or swallowing for example). Scales that measure subjective wellbeing, like the scales we used for general health and quality of life in most chapters, have the advantage of measuring outcomes that are meaningful to patients, but most likely represent different things to different patients. Also, within chronic and/or severe illness, interesting paradoxes have been described that limit their value. One example is the 'response shift theory', a phenomenon in which patients report better quality of life when they are ill, because they appreciate other thing in their lives more than when they were healthy [24]. It is difficult to capture actual outcomes, while preventing circular reasoning in analyzing data. When interpreting results of trials and cohort studies in FMD these are important considerations.

Finally, using self-report is influenced by participant reaction bias, which means patients adjust their answers based on expectations they have concerning the aim of questionnaires. One form, which seems likely to be present in FMD, is called

evaluation apprehension and refers to the concern of being judged based on certain answers [25]. In this thesis, it is likely that underreport of psychiatric symptoms has taken place. Patients that filled out questionnaires (as part of the fMRI studies) in the presence of the investigator, or patients who were questioned over the phone (in the prognosis study (chapter 8) or SHIFT study (chapter 10)), remarked they'd rather not admit to have depressive or anxious symptoms, because they feared this would be linked to the cause of their symptoms. Some indicated that these questions made them suspicious of the purpose of the study and the conviction of the research team on the nature of functional disorders. This in turn might have influenced their appreciation of the studied intervention. Stigma was also assumed be a factor in the explanation as to why FMD patients were less likely to agree that stress or worry was a cause for their symptoms (24% agreed) compared to patients with other neurological conditions (56% agreed, $p<0.001$) in the study by Stone et al that served as a baseline for the follow-up study in chapter 8 [9].

For most studies in this thesis we used the subjective clinical global improvement scale to overcome the difficulty in measuring symptom severity of FMD. Although not fine-grained, this clear 7-point Likert scale covers the average severity over a certain timeframe and thereby overcomes the problem of a snapshot measurement. It is used increasingly in FMD. Our studies would have benefitted from patient interviews and physical examinations alongside questionnaires, as this overcomes both the problem of rating functional co-morbidity and underreport. A recent recommendations paper by the EURONET-SOMA committee on outcome measurement in functional syndromes (comprising somatic symptom disorder, bodily distress disorder and functional somatic syndromes) underlines the value of interviews [26]. However interviews are less objective and cost more time and effort. The recommendations paper furthermore stressed the importance of testing patient satisfaction as an outcome measure, using the question 'Would you recommend this treatment to another person/a friend with similar problems?' In the SHIFT trial, we found patients were highly satisfied with an intervention that did not improve any other predefined outcomes. The intervention met meaningful needs of patients: being justly informed, getting recognition and feeling heard. It is important to realize these are in themselves important endpoints.

FUTURE DIRECTIONS

Like we stated in the introduction, new findings provide new angles for research. Some of these future directions are discussed here.

Mechanism

To extend knowledge on sense of agency within FMD, using augmented/virtual reality is a logical next step. It is a promising way to manipulate sensory input and the experience of motor output, body scheme and attention. Nahab et al were the first to perform such a study in FMD [6]. Several ways to manipulate bottom up experiences of the outside world and the body itself, using either first person or third person perspective, could be studied. The use of virtual reality when studying the pathophysiology of FMD might have the additional benefit of a potential use for treatment interventions. Virtual reality is sometimes used within neurorehabilitation [27], and has been studied sporadically. For motor symptoms in for example stroke and PD, it does not always exceed the effect of real-life exercises [28, 29], although it seems helpful to improve the symptom of neglect after stroke [30]. It is reasonable to suggest virtual reality might be more helpful for motor symptoms in FMD than Parkinson's disease or stroke, because motor expectations, sense of agency and attention play a larger role in FND, and these are presumably more susceptible to the effect of manipulation.

The notion that beliefs, or expectations, are crucial in the pathophysiology of FMD, is one of the reasons why education and cognitive therapy are thought to be effective. They are used to manage and alter beliefs. Within that framework, the role of suggestion in the treatment of FMD is often debated. The role of suggestion within FMD can be studied by looking at hypnosis. FMD patients were found to have higher hypnotic sensitivity [31] and hypnosis is sometimes used in treatment, although this is rarely studied. It has been argued hypnosis can be a model for functional symptoms, in the sense that alterations in mental representation and brain function occur through comparable mechanisms. A statement backed up by finding from imaging studies showing activity in overlapping networks in FND and hypnosis [32, 33]. In a comparable way, suggestion through placebo and nocebo effects have been linked to the mechanism and treatment of FMD. A strong placebo response is often found in treatment studies in FMD and the parallel with nocebo effects and the mechanism of FND has been made [34]. It needs to be noted that the placebo effect is high in all patients, functional and non-functional, and the mechanism behind that might not be any different in other neurological disorders. Also, ethical considerations

need to be taken into account when considering the direct use of suggestion in the approach to a patient with FMD [35]. However, it would be highly valuable to gain more clarity on the exact content of patients' beliefs towards symptoms and treatment and to study the role of suggestion within education. Also, if patients with FMD are indeed more susceptible to suggestion, it is even more important to test treatments for FMD in randomized trials. This is especially relevant for the many treatment strategies that are currently promoted in practice (for example even in alternative medicine), in which the attributed effects are likely largely due to suggestion. All in all, disentangling beliefs, expectations, suggestion and the way education from the neurologist affects these components, will provide us with potentially valuable gateways for treatment of FMD.

Prognosis

No consecutive follow-up studies have been performed in patients with short duration of symptoms, for example presenting at the emergency department, or at the GP. The overall picture of the prognosis of FMD, and generalizability to clinical practice, would benefit greatly from such studies.

The role of education in treatment

As we concluded from the SHIFT study, educating patients on FMD remains an important pillar of treatment. However, although patients were satisfied with our intervention, we found it did not improve outcome on its own.

Anecdotally, we came across several interesting viewpoints from patients, that were not captured by the standardized questionnaires. Some of them were derived from open questions in the SHIFT study, which are shortly summarized in chapter 10. One important observation for example was that patients mentioned that contractionary explanations provided by health care professionals that lacked experience with FMD, hampered the effect the website could have had. Other patients provided reasons for improvement that were not in the standard questionnaire (like a newly born grandchild or changing physiotherapists). Generally, questionnaires are limited by their predefined set of questions, not leaving much room for new insights. Patient interviews could deepen our understanding of FMD. A recent qualitative study by Nielsen et al (2019) did exactly that, and found amongst others that a lack of understanding of their disorder left patients feeling unable to help themselves. The role of education within treatment in particular would be an interesting avenue to explore, for example by interviewing patients that have seen the website from the SHIFT trial. It would be valuable to advance from earlier studies into patients' beliefs,

and to discern health related beliefs into meaningful categories that could be used to tailor (psychological) treatment. For example, in some patients, specific beliefs might need to be challenged before self-help education can be retained, such as a lack confidence in the diagnosis, or strong beliefs in the need for certain tests. These beliefs are most likely heterogenous.

This touches upon the popular theme of personalized medicine or 'patient centered care', which is just as relevant for FMD as for other disorders. Similarities between patients could be targets for treatment, but it might be more helpful to define subgroups that respond to specific interventions that can be used to triage treatment. Defining which factors should be specific targets for therapy would be the first step. There are no studies comparing and triaging subgroups of FMD patients, although many studies apply exclusion criteria, indicating a presumed association between these patient-specific factors and outcome. From our RCT (chapter 10), we found duration of symptoms had a negative effect on outcome. Long symptom duration is generally a poor prognostic sign, but it is potentially even more relevant when providing an education and self-help intervention, which might be more beneficial for patients with a recent diagnosis. Also, our prognostic study (chapter 8) showed somatization disorder at baseline negatively predicted outcome, which might indicate patients with numerous different functional symptoms throughout life are a distinct group. Many factors are conceivably important when designing and assigning therapy, like if symptoms come in attacks or are continuous and if psychopathology is prominent. More research into this area is duly needed.

PERSONAL REFLECTIONS

When working on this thesis, I have had the opportunity to talk to many FMD patients, witness expert physicians in clinic and discuss FND with fellow researchers from several countries. These encounters provided food for thought, not always directly related to the chapters of this thesis. Some of them I would like to share with you.

Firstly, we found neurologists often don't explicitly record their diagnosis of FMD in their clinic letters. As an additional part of the prognostic study in chapter 8 we tried - unfortunately fruitlessly - to collect numbers of hospital visits and the frequency of additional functional symptoms within the follow-up period. However, it was often not clear enough from the medical records if symptoms were diagnosed to be functional or not. When the described type and course of symptoms was

indicative of a functional cause, terminology used in the records was often vague or only the excluded diagnoses were listed. It is very likely these physicians did not discuss, let alone explain, the diagnosis to their patients either. This is not only a clear disadvantage when aiming for transparency between health care professionals. It also shows that many neurologists still feel insecure on how to determine the diagnosis, or how to explain it.

Secondly, from personal experience when talking to patients involved in the studies in this thesis and when presenting data on functional symptoms for neurologists or psychiatrists, it became clear that dualistic thinking is still very much ingrained in the thinking of both lay-people and physicians. It is very difficult to overcome as long as psychiatry and neurology are considered separate specialties and disorders are categorized as either psychiatric or neurological. Dualistic thinking triggers clear problems in the approach to the patient. Having a psychiatric disorder is considered taboo to begin with and therefore an explanation of FMD including psychological factors is often considered problematic. However, that could be overcome like in other psychiatric disorders. The main problem is the (wrong) assumption that is often made, that psychiatric disorders as opposed to neurological disorders, would be willed. Or in other words, when it is discussed with patients that psychological factors (often oversimplified called 'stress') might play a role in the origin of their symptoms, they feel accused of putting it on. This in turn inhibits an open conversation about the cause of FMD and the influencing factors that could be important in treatment. Paradoxically, the majority of patients do accept that there are many factors influencing health and wellbeing, including emotional states, stressful events and past experiences. As long as it is not implied their symptoms are feigned, I have found they are very willing to investigate the role of psychological factors as one of the factors that contributed to the disorder or as a potential focus for treatment. It would be very helpful if health care professionals would be more aware of this pitfall. By explaining to patients that their symptoms are genuine, that body and mind are one, and that many different factors can cause, trigger or sustain the symptoms, this problem is usually easily overcome. Perhaps needless to say, the same holds true for all other disorders (dualistically framed as 'organic'). Perhaps the Dutch idiom 'tussen de oren' ('between the ears, an expression used figuratively to indicate a psychological cause) should be taken more literally: it's all coming from the brain.

Thirdly, our review highlights there is now some evidence of effective treatments for FMD. The most promising approach is specialized physiotherapy, which includes education and movement retraining aimed to restore normal movement [12, 36].

Furthermore, multidisciplinary rehabilitation was proven to be effective [37, 38]. Unfortunately, there is a large gap between needs and availability of treatment, internationally [39] as well as in the Netherlands, as noted by several patients that participated in the SHIFT study (chapter 10). Despite the potential reversibility and the growing load of effective rehabilitation studies, rehabilitation services in the Netherlands mostly reject patients with FMD. Involvement of rehabilitation physicians in the research field and in clinical practice is much desired. Also, there remains a great need for specialized therapists (physiotherapy, occupational therapy, psychology), who figuratively speak the same language. A Dutch network of specialists in which ideally physiotherapists, neurologists, occupational therapists, rehabilitation physicians, psychologists and patients share their knowledge and experience, would be an important step forward.

Finally, I came to realize that physicians and patients often have very different priorities and/or perspectives, sometimes causing misunderstandings or even harm. This is most prominent in the acute setting: when a patient presents with acute onset neurological symptoms, doctors want to rule out serious and/or life-threatening conditions first and fast. For a patient the testing and investigations that happen quickly without much explanation are often perceived out of their control, or even scary, and at the very least they suggest something serious must be going on. Once the doctor has ruled out these serious conditions, their immediate attention is no longer required and they often need to attend another acute patient. Leaving the patient without a clear explanation of what is going on, while they still experience the symptoms that were taken so seriously earlier. The uncertainty or anxiety resulting from such an experience can become a perpetuating factor. Furthermore, I have learned that patients often reason that severe symptoms (like tremor with a big amplitude or a severe headache), are most likely caused by serious disorders (potentially life-threatening or neurodegenerative disorders). Physicians do not recognize this. They have learned to look for specific red flags that can be subtle and usually not recognized by the patient as being alarming. Because of this clear difference in priorities, patients are often not reassured by the explanation provided. Also, partly to my surprise, belief systems about causes for the disorder (like Lyme disease or specific foods), or possible solutions (like alternative medicine), can co-exist with a clear understanding of the explanation given by the physician on FND. Beliefs are often irrational. Physicians, trained to think in a very rational manner, should be aware of these belief systems and question their patients about them, as it is often important to counter them in order to start any treatment.

'After all, clinical medicine is above all the study of the difficult aspects and complexities of diseases. When a patient calls on you, he is under no obligation to have a simple disease just to please you.'
Charcot 1888 [40]

REFERENCES

1. Kalkman JS, Zwarts MJ, Schillings ML, van Engelen BGM, Bleijenberg G. Different types of fatigue in patients with facioscapulohumeral dystrophy, myotonic dystrophy and HMSN-I. Experienced fatigue and physiological fatigue. Neurol Sci. 2008;29 SUPPL. 2:238–40.
2. Moore JW, Middleton D, Haggard P, Fletcher PC. Exploring implicit and explicit aspects of sense of agency. Conscious Cogn. 2012;21:1748–53. doi:10.1016/j.concog.2012.10.005.
3. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;:700–11.
4. De Jong BM. Neurology of widely embedded free will. Cortex. 2011;47:1160–5. doi:10.1016/j.cortex.2011.06.011.
5. Pesaran B, Nelson MJ, Andersen RA. Free choice activates a decision circuit between frontal and parietal cortex. Nature. 2008;453:406–9.
6. Nahab FB, Kundu P, Maurer C, Shen Q, Hallett M. Impaired sense of agency in functional movement disorders : An fMRI study. 2017;:8–11.
7. Maurer CW, Epstein SA, Hallett M. Impaired self-agency in functional movement disorders A resting-state fMRI study. 2016;:1–8.
8. Boeckle M, Liegl G, Jank R, Pieh C. Neural correlates of conversion disorder: Overview and meta-analysis of neuroimaging studies on motor conversion disorder. BMC Psychiatry. 2016;16:1–15.
9. Stone J, Warlow C, Sharpe M. The symptom of functional weakness: A controlled study of 107 patients. Brain. 2010;133:1537–51. doi:10.1093/brain/awq068.
10. Stone J, Smyth R, Carson A, Lewis S, Prescott R, Warlow C, et al. Systematic review of misdiagnosis of conversion symptoms and "hysteria". BMJ. 2005;331:989. doi:10.1136/bmj.38628.466898.55.
11. Stone J, Carson a., Duncan R, Coleman R, Roberts R, Warlow C, et al. Symptoms "unexplained by organic disease" in 1144 new neurology out-patients: how often does the diagnosis change at follow-up? Brain. 2009;132:2878–88. doi:10.1093/brain/awp220.
12. Nielsen G, Buszewicz M, Stevenson F, Hunter R, Holt K, Dudziec M, et al. Randomised feasibility study of physiotherapy for patients with functional motor symptoms. 2016;:1–7.
13. Erro R, Brigo F, Trinka E, Turri G, Edwards MJ, Tinazzi M. Psychogenic nonepileptic seizures and movement disorders: A comparative review. Neurol Clin Pract. 2016;6:138–49. doi:10.1212/CPJ.0000000000000235.
14. Kanaan RAA, Duncan R, Goldstein LH, Jankovic J, Cavanna AE. Are psychogenic non-epileptic seizures just another symptom of conversion disorder? J Neurol Neurosurg Psychiatry. 2017;88:425–9.
15. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet. 1999;354:936–9.
16. Ekanayake V, Kranick S, LaFaver K, Naz A, Frank Webb A, LaFrance WC, et al. Personality traits in psychogenic nonepileptic seizures (PNES) and psychogenic movement disorder (PMD): Neuroticism and perfectionism. J Psychosom Res. 2017;97 November 2016:23–9. doi:10.1016/j.jpsychores.2017.03.018.
17. Fukushima H, Goto Y, Maeda T, Kato M, Umeda S. Neural substrates for judgment of self-agency in ambiguous situations. PLoS One. 2013;8.

18. Kal EC, Van Der Kamp J, Houdijk H. External attentional focus enhances movement automatization: A comprehensive test of the constrained action hypothesis. Hum Mov Sci. 2013;32:527–39. doi:10.1016/j.humov.2013.04.001.

19. Ejareh dar M, Kanaan RAA. Uncovering the etiology of conversion disorder: Insights from functional neuroimaging. Neuropsychiatr Dis Treat. 2016;12:143–53.

20. van der Kruijs SJM, Bodde NMG, Vaessen MJ, Lazeron RHC, Vonck K, Boon P, et al. Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures. J Neurol Neurosurg Psychiatry. 2012;83:239–47. doi:10.1136/jnnp-2011-300776.

21. Perez DL, Dworetzky BA, Dickerson BC, Leung L, Cohn R, Baslet G, et al. An integrative neurocircuit perspective on psychogenic nonepileptic seizures and functional movement disorders: Neural functional unawareness. Clin EEG Neurosci. 2015;46:4–15.

22. Nielsen G, Ricciardi L, Meppelink AM, Holt K. CLINICAL PRACTICE A Simpli fi ed Version of the Psychogenic Movement Disorders Rating Scale : The Simpli fi ed Functional Movement Disorders Rating Scale (S-FMDRS). Mov Disord Clin Pract. 2017; September 2016:1–7.

23. Shipston-Sharman O, Hoeritzauer I, Edwards M, Reuber M, Carson A, Stone J. Screening for functional neurological disorders by questionnaire. J Psychosom Res. 2019;119 September 2018:65–73. doi:10.1016/j.jpsychores.2019.02.005.

24. Schwartz CE, Andresen EM, Nosek MA, Krahn GL. Response Shift Theory: Important Implications for Measuring Quality of Life in People With Disability. Arch Phys Med Rehabil. 2007;88:529–36.

25. Pelhan B, Blanton H. Conducting research in psychology. Measuring the weight of smoke. 3rd Ed Thomson Whatsworth. 2007.

26. Rief W, Burton C, Frostholm L, Henningsen P, Kleinstäuber M, Kop WJ, et al. Core Outcome Domains for Clinical Trials on Somatic Symptom Disorder, Bodily Distress Disorder, and Functional Somatic Syndromes: European Network on Somatic Symptom Disorders Recommendations. 2017.

27. O'Neil O, Fernandez MM, Herzog J, Beorchia M, Gower V, Gramatica F, et al. Virtual Reality for Neurorehabilitation: Insights From 3 European Clinics. PM R. 2018;10:S198–206.

28. Saposnik G, Cohen LG, Mamdani M, Pooyania S, Ploughman M, Cheung D, et al. Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial. Lancet Neurol. 2016;15:1019–27. doi:10.1016/S1474-4422(16)30121-1.

29. Yang WC, Wang HK, Wu RM, Lo CS, Lin KH. Home-based virtual reality balance training and conventional balance training in Parkinson's disease: A randomized controlled trial. J Formos Med Assoc. 2016;115:734–43. doi:10.1016/j.jfma.2015.07.012.

30. Pedroli E, Serino S, Cipresso P, Pallavicini F, Riva G. Assessment and rehabilitation of neglect using virtual reality: a systematic review. Front Behav Neurosci. 2015;9 August:1–15. doi:10.3389/fnbeh.2015.00226.

31. Roelofs K, Hoogduin KAL, Keijsers GPJ, Näring GWB, Moene FC, Sandijck P. Hypnotic susceptibility in patients with conversion disorder. J Abnorm Psychol. 2002;111:390–5.

32. Vuilleumier P. Brain circuits implicated in psychogenic paralysis in conversion disorders and hypnosis. Neurophysiol Clin. 2014;44:323–37. doi:10.1016/j.neucli.2014.01.003.

33. Deeley Q. Hypnosis as a model of functional neurologic disorders. Handb Clin Neurol. 2016;139:95–103. doi:10.1016/B978-0-12-801772-2.00009-6.

34. Carlino E, Piedimonte A, Benedetti F. Nature of the placebo and nocebo effect in relation to functional neurologic disorders. Handb Clin Neurol. 2016;139:597–606. doi:10.1016/B978-0-12-801772-2.00048-5.

35. Rommelfanger KS. Opinion: A role for placebo therapy in psychogenic movement disorders. Nat Rev Neurol. 2013;9:351–6. doi:10.1038/nrneurol.2013.65.

36. Nielsen G, Stone J, Matthews A, Brown M, Sparkes C, Farmer R, et al. Physiotherapy for functional motor disorders: a consensus recommendation. J Neurol Neurosurg Psychiatry. 2014;:jnnp--2014.

37. McCormack R, Moriarty J, Mellers JD, Shotbolt P, Pastena R, Landes N, et al. Specialist inpatient treatment for severe motor conversion disorder: a retrospective comparative study. J Neurol Neurosurg Psychiatry. 2014;85:895–900. doi:10.1136/jnnp-2013-305716.

38. Jordbru AA, Smedstad LM, Klungsoyr O, Martinsen EW. Psychogenic gait: a randomized controlled trial on effect on rehabilitation. Clin Rehabil. 2012;In submiss.

39. Espay AJ, Goldenhar LM, Voon V, Schrag A, Burton N, Lang AE. Opinions and clinical practices related to diagnosing and managing patients with psychogenic movement disorders: An international survey of movement disorder society members. Mov Disord. 2009;24:1366–74.

40. Charcot J-M. Syphilis, locomotor ataxia, facial paresis. Charcot, the Clinician: The Tuesday Lessons. In: New York: Raven Press. 1888. p. 1–25.

Nederlandse samenvatting

Functionele motorische stoornissen (FMS) bestaan uit onwillekeurige bewegingen, houdingsveranderingen, loopstoornissen en parese. Ze worden gekenmerkt door specifieke afwijkingen in het neurologisch onderzoek en aanknopingspunten in de anamnese, die passen bij de functionele aard van de klachten, zoals variabiliteit, invloed van aandacht en afleiding en incongruentie met anatomische grenzen. FMS komen vrij veel voor; geschat wordt dat rond de 15-30% van de patiënten op de poli neurologie een functionele stoornis heeft. De stoornissen geven vaak ernstige beperkingen en een verminderde kwaliteit van leven, vergelijkbaar met de ziekte van Parkinson en Multipele Sclerose.

Het onderzoeksveld was aan het begin van dit proefschrift in hoog tempo aan het veranderen. Nieuwe inzichten veranderden de leidende theorieën over het mechanisme, de diagnose en de aanpak van patiënten met FMS. Deze ontwikkelingen waren cruciaal voor de opzet van dit onderzoek, dat zicht heeft gericht op het mechanisme, de prognose en de behandeling van FMS.

DEEL 1. PATHOFYSIOLOGIE

Om FMS beter te begrijpen zijn zowel klinische observatiestudies als experimentele studies nodig. Klinische observatie geeft inzicht in mogelijke onderliggende mechanismen en genereert nieuwe hypothesen. Experimentele studies kunnen die specifieke hypothesen toetsen. Dit proefschrift beschrijft een aantal studies die de pathofysiologie van beide kanten belichten.

Klinische observatiestudies

Het klinische beeld van FMS is heterogeen wat betreft risicofactoren, triggers en co-morbiditeit. Daarnaast zijn de symptomen veranderlijk: binnen dezelfde patiënt veranderen het type symptoom, de ernst en lokalisatie van de klachten regelmatig. Ondanks dat er niet veel systematische studies zijn gedaan, wordt wel beschreven dat veel patiënten met FMS ook andere functionele en psychiatrische symptomen hebben. Daarbij is er een groeiend besef dat niet-motorische symptomen een belangrijk aandeel hebben in de beperkte kwaliteit van leven van patiënten met FMS. Hoofdstuk 1 en 2 zijn gebaseerd op baseline data van patiënten met FMS die deelnamen aan de SHIFT trial, beschreven in hoofdstuk 10.

Hoofdstuk 1 beschrijft een vergelijking tussen 160 patiënten met verschillende functionele motor symptomen. Deze werden ingedeeld in groepen op basis van

hun dominante motor symptoom, bepaald door de verwijzend neuroloog. Dit resulteerde in groepen patiënten met als dominant symptoom tremor, myoclonus, dystonie, parese of loopstoornis. Verschillen in demografie, de manier waarop de symptomen begonnen, niet-motore symptomen, kwaliteit van leven en functioneren, en de aanwezigheid van andere functionele motor symptomen werden onderzocht tussen de groepen. Het merendeel van deze uitkomstmaten was niet verschillend tussen de groepen. Fysiek functioneren was sterker beperkt in patiënten met een loopstoornis en parese dan in alle andere groepen. Beperkingen in werk en sociaal functioneren werden meer gerapporteerd door patiënten met loopstoornissen en parese dan door patiënten met myoclonus. Veel patiënten rapporteerden naast het hoofdsymptoom ook andere motore symptomen. Deze bevindingen suggereren dat er veel overlap is tussen verschillende functionele motor symptomen, wat mogelijk ook geldt voor het onderliggende mechanisme en de manier waarop ze zouden moeten worden behandeld.

In de spreekkamer blijkt vaak dat patiënten met FMS veel last hebben van vermoeidheid. In **hoofdstuk 2** is onderzocht hoe ernstig die vermoeidheid is in een groep van 181 patiënten met functionele motor stoornissen vergeleken met een groep van 217 patiënten met een neuromusculaire ziekte uit een bestaand cohort. Hierbij is gebruik gemaakt van de Checklist Individual Strength (CIS) vragenlijst, die vier subdomeinen van vermoeidheid onderzoekt; ernst van de vermoeidheid, motivatie, concentratie, fysieke activiteit. Patiënten met FMS hadden een hogere score dan patiënten met neuromusculaire ziekten op alle subdomeinen. Er was sprake van ernstige vermoeidheid, gedefinieerd als een CIS-score van 35 of hoger, in 78% van de patiënten met FMS, vergeleken met 53% van de patiënten met neuromusculaire ziekten. Daarnaast had vermoeidheid een significant effect had op de algehele gezondheid die patiënten zelf hadden gerapporteerd, terwijl de ernst van de functionele motor symptomen daar geen significant effect op had. Vermoeidheid bleek gecorreleerd aan ernst van de functionele motor symptomen, depressie en angst. Op basis van die bevindingen lijkt vermoeidheid zowel een co-morbide symptoom van FMS als een gevolg van (chronische) multi-morbiditeit.

In **hoofdstuk 3** zijn de niet-motore symptomen onderzocht in twee groepen patiënten, namelijk 16 patiënten met functionele myoclonus en 23 patiënten met corticale (organische) myoclonus. Symptomen van vermoeidheid, depressie en angst kwam net zo veel voor bij functionele als corticale myoclonus. Het enige verschil tussen de groepen was dat er meer pijn werd gerapporteerd in de functionele groep. Daarnaast bleek de ernst van de motore symptomen in de functionele groep gecorreleerd

te zijn aan angst en depressie, terwijl dat in de corticale myoclonus groep niet zo was. Ondanks de kleine groep die voornamelijk uit de derde lijn kwam, wat de nodige beperkingen met zich meebrengt, was de conclusie dat psychiatrische co-morbiditeit veel voorkomt in beide groepen. Dat spreekt veelgehoorde ideeën over hogere prevalentie van psychiatrische symptomen in FMS tegen. De hoge prevalentie in beide groepen betekent echter wel dat er aandacht moet zijn voor niet-motore verschijnselen bij FMS in de klinische praktijk.

Experimentele studies

De experimentele studies in dit proefschrift waren gericht op de beleving van controle over beweging ('sense of agency'), aandacht voor het lichaam en afwijkingen in het lichaamsschema.

In **hoofdstuk 4** beschrijven we een experiment gericht op controle over beweging. Negentien patiënten met FMS en evenveel gezonde controle personen voerden een motorische taak uit, waarin de feedback die deelnemers ontvingen na het bewust drukken op een knop werd gemanipuleerd. De manipulatie bestond uit een variabele vertraging tussen actie en reactie (geluidssignaal na indrukken van de knop). Deelnemers werd vervolgens gevraagd of zij het geluid hadden veroorzaakt of niet. De hypothese was dat patiënten met FMS minder gevoel van controle zouden hebben over de beweging, maar dat kwam niet uit het experiment. Na analyse van alle reacties bleken er geen verschillen tussen de groepen te zijn. We concludeerden dat er nog steeds sprake zou kunnen zijn van een verstoring van het gevoel controle te hebben over beweging (sense of agency), maar dat ons experiment gericht was op een expliciet gevoel van controle, terwijl bij FMS mogelijk impliciete controle verstoord is.

In zowel hoofdstuk 5 en 6 worden fMRI studies beschreven, uitgevoerd in een groep patiënten met functionele myoclonus of tremor, vergeleken met gezonde controles van dezelfde leeftijd en geslacht.

Hoofdstuk 5 beschrijft de uitkomsten van een taak-gebonden fMRI experiment. In de actie-selectie taak moesten de deelnemers wisselend zelf kiezen, of er werd hen opgelegd, met welke vinger ze een knop moesten indrukken, of op welke knop ze moesten drukken. Hierdoor konden we het verschil tussen opgelegde motor actie en vrije keus aan de ene kant, en lichaamsschema (keuze voor een vinger) ten opzichte van doelgerichte actie (keuze van een knop) vergelijken. Eerdere bevindingen in gezonde deelnemers werden bevestigd: prefrontale en pariëtale activatie is geassocieerd met vrije ten opzichte van vastgelegde selectie. In de vinger

ten opzichte van knop selectie vonden we activatie van de occipitaal en anterieure pariëtaal cortex, inclusief de postcentrale sulcus. In FMS vonden we ten opzichte van gezonde controles een verminderde activatie van de linker primaire motor cortex in alle motorische taken. In de praktijk hebben patiënten vaak moeite met het uitvoeren van eenvoudige motorische taken, daarom zou deze bevinding kunnen passen bij verstoorde expliciete controle over beweging. De linker insula toonde verminderde activiteit in vrije vinger selectie in FMS en dit was ook gecorreleerd met ernst van de symptomen. Deze resultaten bevestigen de hypothese dat verstoringen in het gevoel controle te hebben over beweging (sense of agency) en in de perceptie van lichaamsschema optreden in patiënten met FMS.

In **hoofdstuk 6** worden de resultaten beschreven van een data-gedreven exploratieve 'resting state' studie. In een dergelijke studie voeren patiënten geen taak uit tijdens de fMRI scan, maar worden patronen van activatie in de hersenen bekeken die met elkaar samenhangen op basis van connectiviteit. De studie vergelijkt patronen tussen 17 patiënten met functionele tremor of schokken en 17 gezonde controles. De analyse-methode 'independent component analysis' is hierbij toegepast. Na selectie van componenten passend bij een vooropgestelde hypothese, werden de groepen vergeleken met een aantal statistische testen. We vonden veranderde activatie in een component bestaande uit de (pre)cuneus en gyrus cinguli (posterior) in de fluctuaties van lagere range frequenties. De betekenis van die frequentie fluctuaties is nog niet geheel opgehelderd; wel is bewezen dat ze correleren met hersenactiviteit en met andere maten van connectiviteit. De (pre)cuneus en andere midline structuren zijn geassocieerd met een verstoring van het gevoel controle te hebben over beweging (sense of agency), wat eerdere theorieën over functionele stoornissen zou bevestigen. Er waren geen andere verschillen tussen de groepen.

DEEL 2. PROGNOSE

Deel 2 van dit proefschrift beschrijft het natuurlijk beloop van FMS, door middel van een systematische review van de literatuur (**hoofdstuk 7**) en een grote lange-termijn follow-up studie in FMS (**hoofdstuk 8**).

In de systematische review van de literatuur werden 24 studies geïncludeerd die voornamelijk retrospectieve gegevens over het natuurlijk beloop van FMS bevatten. De studies waren erg heterogeen in aantal patiënten, duur van de follow-up (0.5 tot 19 jaar) en klinische setting. Gemiddeld over alle studies was 39% van de patiënten

(10-90%) na de follow-up periode slechter of hetzelfde voor wat betreft de motorische symptomen; 20% van de patiënten was geheel hersteld. Daarbij gingen verminderde kwaliteit van leven en beperkingen van het dagelijks leven hand in hand met een slechte prognose van de motorische symptomen.

De follow-up studie was een case-control studie met drie groepen: patiënten met functionele parese, een controlegroep met andere neurologische aandoeningen die parese veroorzaken en een gezonde controlegroep. De follow-up duur was 14 jaar. Net als in de systematische review was ook in onze studie 20% van de patiënten in de functionele groep compleet hersteld. Vergeleken met de controle groep van neurologische aandoeningen verbeterden meer patiënten met functionele parese. Echter, de meeste secundaire uitkomstmaten (zoals algehele gezondheid, fysiek functioneren en werk) waren gelijk in beide groepen, en duidelijk slechter dan de gezonde controlegroep.

Misdiagnose was zeldzaam: bij één patiënt met FMS en één patiënt uit de groep met een andere neurologische aandoening bleek gedurende de follow-up de initiële diagnose onjuist te zijn geweest.

Het aantal patiënten dat tijdens de follow-up periode overleed was hoger in de functionele parese groep dan in de gezonde populatie in diezelfde periode in hetzelfde demografische gebied (Lothian, Schotland). De doodsoorzaak had in geen van deze gevallen direct te maken met de functionele parese. Gezien de kleine groep in totaal (11 patiënten) moeten de resultaten van deze bevinding voorzichtig worden geïnterpreteerd. Een mogelijke verklaring van dit verschil met de normale populatie is dat het hebben van een chronische aandoening waarschijnlijk negatieve gevolgen heeft voor de algehele gezondheid, werk en daarmee economische situatie van patiënten.

In beide studies was het moeilijk om prognostische factoren te bepalen. In de systematische review werden een aantal positief voorspellende factoren in meerdere studies gevonden: korte duur van de symptomen, vroege diagnose en tevredenheid met de zorg. Geslacht had geen invloed op de uitkomst. Een late diagnose en de aanwezigheid van een persoonlijkheidsstoornis waren gecorreleerd met een slechte uitkomst.

In onze follow-up studie vonden we alleen univariabele voorspellers voor slechte uitkomst: somatisatiestoornis, slechte algehele gezondheid, pijn en het totaal aantal symptomen bij inclusie hadden een negatief voorspellende waarde voor de uitkomst

van de parese. Deze bleven niet bestaan als ze voor elkaar werden gecorrigeerd in een multivariabel model.

De belangrijkste beperking van beide studies was dat het merendeel van de patiënten al lang symptomen had voor ze geïncludeerd werden, terwijl dat uit diezelfde studies naar voren komt als negatieve voorspeller van het beloop. Daarom zijn de bevindingen mogelijk niet te generaliseren naar een populatie met acute symptomen.

DEEL 3 BEHANDELING

Er is weinig wetenschappelijk onderzoek gedaan naar de behandeling van FMS. In **hoofdstuk 9** hebben we de literatuur hierover samengevat. Hieruit blijkt dat een aanpak waarin patiënten uitleg krijgen over de diagnose en waarin normale bewegingen opnieuw worden getraind, soms in combinatie met psychologische behandeling, effectief kan zijn. Voor de effectiviteit van psychologische behandeling alleen is weinig wetenschappelijk bewijs. Ondanks dat een aanpak bestaande uit verschillende stappen (uitleg, eerstelijnstherapie, multidisciplinaire therapie) wordt aanbevolen, is dit in de praktijk nog niet altijd haalbaar, aangezien gespecialiseerde zorgaanbieders schaars zijn.

In de gerandomiseerde onderzoek met controlegroep (RCT) in **hoofdstuk 10** is het effect van online educatie en zelfhulp als toevoeging op de normale zorg onderzocht, vergeleken met alleen normale zorg. 186 patiënten met FMS werden gerandomiseerd in twee groepen: met en zonder toegang tot de speciaal samengestelde website. Er waren geen verschil tussen de groepen op de hoofduitkomstmaat, algehele gezondheid (zelf-gerapporteerd) op de Clinical Global Improvement schaal op 3 en 6 maanden na aanvang van de studie. Ook waren er geen verschillen op de secundaire uitkomsten, zoals ernst van de functionele symptomen, co-morbiditeit, of begrip van de diagnose. Patiënten waren wel erg tevreden over de informatie op de website. In het gehele cohort (de twee groepen bij elkaar) was een significante correlatie tussen vertrouwen in de diagnose en algehele gezondheid, wat het belang van educatie in het algemeen benadrukt en onze hypothese bevestigt dat educatie een relevant onderdeel is van de behandeling. De belangrijkste limitatie was selectie bias, die zowel op het niveau van de verwijzend neuroloog als van de patiënten heeft plaatsgevonden. Omdat er geen verschillen tussen de groepen werden gevonden, werd geconcludeerd dat educatie en zelfhulp zonder begeleiding van een therapeut als losstaande interventie niet effectief is in FMS.

Dankwoord

Mijn PhD-traject heb ik als een hele waardevolle periode ervaren en daar hebben heel veel mensen aan bijgedragen.

Allereerst wil ik graag alle patiënten met een functionele stoornis en gezonde vrijwilligers bedanken die hebben willen deelnemen aan de verschillende studies in deze thesis. Bedankt voor jullie hulp en geduld, en voor alle nieuwe inzichten die we hebben gekregen. Uiteraard ook grote dank voor de fondsen die het onderzoek mogelijk gemaakt hebben: de GSMS graduate school van de RUG voor financiering van mijn PhD-project, de de Cock-stichting, voor subsidie van het MRI-project, de UMCG Pilot Doelmatigheid HAP subsidie, voor financiering van de pilotstudie voorafgaand aan de SHIFT studie en stichting MIND (voorheen Fonds Psychische Gezondheid), voor de subsidie van de SHIFT studie.

Marina, Jon, Judith and Alan. What you all share is curiosity, passion and above all a good sense of humor, which has made this trajectory above all a lot of fun.

Marina, je persoonlijke aandacht en (Haagse) humor maken dat het vanaf het begin ontzettend vertrouwd is geweest om bij je binnen te lopen, en om samen van alles te organiseren. Je gunt het ons (je PhDs) om te delen in jouw netwerk, om onze eigen fouten te durven maken en stimuleert ons om ervoor te gaan. Jouw pragmatische insteek heeft me altijd op het goede moment ingeperkt waar ik de neiging kon hebben 'oeverloos' te worden. Ik kan me geen betere begeleider bedenken.

Jon, you have inspired me to start this PhD. It's admirable how you've put the topic of FND on the map and are now (one of?!) the world expert(s) in the field. I think our field is the most intriguing part of medicine. So thanks for paving the way! Also, I've found you to be a supportive, understanding, openminded and funny supervisor. You can be kind and critical at the same time, which is admirable. Thank you so much for all that.

Judith, jij hebt altijd weer een verrassende invalshoek, geeft de meest opbouwende kritiek en je hebt pijnlijk vaak gelijk, wat mijn proefschrift heel veel heeft verbeterd.

Alan, your humor, experience, and your skill to give feedback in such a way that I never felt I'd done anything wrong, has been a great help in the process, many thanks.

Members of the examining committee**, professor Mark Edwards, professor Teus van Laar, professor Odile van den Heuvel, professor Theo Bouwman, professor Joke Spikma, professor Peter van Harten and dr. Lineke Tak** thank you for your critical appraisal of this thesis, I am looking forward to the defence.

Lenny, Julia, Martijn, Jona, Romy: bedankt voor het vele werk dat jullie gedaan hebben en voor de kritische vragen: ik heb me regelmatig gerealiseerd dat ik de beste (en leukste) studenten van de afdeling had!

Co-auteurs, bedankt voor de prettige samenwerking. In het bijzonder: **Bauke**, heel erg bedankt voor je optimistische en gedegen manier van begeleiden. Ondanks de vele keren dat alles toch weer anders was, was jij altijd in de stemming om het er nog maar weer eens over te hebben. Ik heb daar veel van geleerd! **Jan-Bernard**, ook jij bent altijd wel weer beschikbaar, en hebt me regelmatig op het laatste moment nog uit de brand geholpen. Bedankt daarvoor! **Hans** bedankt voor al je hulp met de MRI analyses en matlab-scriptjes!! **Anita en Judith**. Bedankt voor jullie geduld iedere keer te wachten tot het 'alleen luisteren'-blok voorbij was om te zien of mensen überhaupt wel iets konden horen. En voor jullie hulp natuurlijk. **Martijn**: bedankt voor het kritische meedenken op velerlei gebied. **Ruben Maalman**, veel dank voor het maken van de getekende filmpjes voor de websites en de getekende samenvattingen in dit boekje. **Sam Hoevenaar**, bedankt voor het maken van de videos voor de website.

Rien Vermeulen en Gerty Casteelen bedankt dat jullie (los van elkaar) de interesse voor functionele stoornissen in mij gewekt en gestimuleerd hebben.

Kamer V4.105. Het zou een variant van het Stockholm-syndroom kunnen zijn, maar als je jarenlang in dezelfde kamer onderzoek zit te doen, blijkt dat je hoe dan ook vrienden wordt. Ik zal het poep-buisje van **Jeffrey** ('dit buisje is de nieuwste ontwikkeling op poep-sampling gebied!'), de liefde voor excell ('weet je waar ik echt van kan genieten? een nette tabel!') van **Hans**, de eeuwige tegenspraak van **Gerrit** ('Niet zo nuanceren, Jeannette, daar houd ik niet van'), de vaak verrassende humor van **Jonathan** ('Ha meneer, ik wilde u gisteren bellen, maar uh, ik bel vandaag'), het enthousiasme voor zowel de ziekte van Parkinson als het Nederlandse levenslied (Wij zijn het derde..) van **Robbert**, de passie voor het zwabberbeen (wat extra goed

klinkt met een Canadees accent) van **Beorn** en de persoonlijke analyses met **Sterre** ('tja, met je ogen dicht, zie je het niet aankomen') missen!

Lieve **Wieke en Anouk:** wij hebben door de jaren heen zoveel meegemaakt dat ik niet weet waar te beginnen, alle gesprekken in V4.105, de vele bewegingsstoornissen projecten, (werk)weekendjes, gedeelde hotelkamers en daarmee gepaard gaande nachtelijke gesprekken. Ik hoop dat we dat gewoon voortzetten, ook al zien we elkaar niet meer elke dag. Heel veel dank.

Lieve **Arthur**, we hebben samen gestudeerd, maanden samen in een kamertje op de KNF in het AMC gezeten en het talent ontwikkeld om allebei tegelijk zowel te praten als te luisteren. Ik denk dat jij mij het meest hebt gevormd als dokter en onderzoeker (of misschien leken we altijd al op elkaar?), en dat bevalt me wel.

Lieve **Myrthe**, wat hebben wij veel gedeeld aan de Paramaribostraat en de Archimedesweg! Ondanks onverstandige keuzes en ingewikkelde overwegingen heb jij er toch altijd wel iets zinnigs en liefs over te zeggen, heel erg bedankt daarvoor.

Anne-Marthe, Anne, Gerrit en Yasmine: jullie als mede-onderzoekers naar functionele stoornissen bedankt voor jullie enthousiasme en interessante bespiegelingen **Anne**: voor onze fijne tijd samen in Edinburgh en gezellige samenwerking op de poli! **Gerrit:** heel erg leuk dat we nu samen op één dag promoveren en er een functionele dag van maken.

FRG (Functional Research Group) Edinburgh: **Lea, Ingrid, Paula, Laura**: It is great to share our enthusiasm for clearly the most interesting topic in the world. What a lovely, supportive group of people you are. I'm so thankful to have been part of that. I am missing the Thursday FRG meetings in the room with the horrible carpet. **Glenn**: definitely a support to know that you've struggled with the same things, but kept your enthusiasm! **Trish,** as a proud member of 'your functional lot' (as you tend to call us these days) I've had such a lovely time at North Park Terrace with you. Thank you for your patience with my late and ever changing planning.

De andere neuro-PhDs, **Arnoud, Dan, Danique, Sygrid, Madelein, Marja, Myrthe d K, Sanne, Rodi, Martje, Marenka, Marieke, Marouska** het staat al in elk dankwoord van onze inmiddels indrukwekkende reeks: alle (noodstroom/submit/reject/etc) borrels, retraites naar Londen, Utrecht, Haarlem en Edinburgh en onze gezamenlijke congressen zorgden voor een onvergetelijke tijd. Sanne ook dank voor het feit

dat jij mij vroeg of ik met jou op tennisles wilde (we kennen beiden het briljante eindresultaat van onze inspanningen). Arnoud voor de nodige rechtse tegenspraak en relativering. Marja en Madelein juist voor alles wat ik met jullie eens ben. Sygrid voor je voorbeeld in doorzettingsvermogen. Myrthe (de K.) voor het aanvoeren van het geheel. Dan voor je droge humor. Danique voor je enthousiasme. Rodi en Martje voor jullie voorbeeld hoe vanalles te combineren én leuk te blijven.

Massimo, Cécile, Michele, Gerd and Wieke: thanks for the amazing days and mostly nights at several movement disorders events. I hope we'll see a lot more of each other when we grow old and wise (or just old).

Lieve vrienden. **Carmen.** Ondanks onze moeizame start (als kleuter vond jij mij suf en ik jou raar), ben ik nu bij jou het meest mezelf. Bedankt voor jouw positieve inslag en humoristische kijk op het leven, daarmee help je me vaak enorm en wordt er in ieder geval genoeg gelachen. **Sanne.** Dank voor jouw nooit aflatende steun, het eeuwige logeeradres en je altijd verfrissende blik. Ik heb mooie herinneringen aan je bezoek aan Edinburgh. **Floor**, ik heb veel bewondering voor jouw nuchtere houding en doorzettingsvermogen. **Ester, Mauro, Anna**, super bedankt voor het tweede thuis in Amsterdam en interesse, Mauro voor je hulp met de introductie! **Joëtta.** Wat hebben wij een ontzettend lange geschiedenis samen. Bedankt voor je lieve interesse en je voorbeeld om keuzes te durven maken voor waar je passie ligt. **Jort.** Dat jij vrij regelmatig op de plek uitkomt waar ik toevallig ook ben, en dat wij steeds onze ervaringen kunnen delen, geeft mij veel vertrouwen. **Reinier,** bijzonder hoe vaak jij zegt wat ik bedoel en prettig dat je me stimuleert om het hoe dan ook maar gewoon te gaan doen allemaal. **Sebastiaan en Jill**, veel dank onze lange vriendschap en vele mooie momenten. **Peter en Nicolette** en met jullie de hele gemeenschap Watergraafsmeer, bedankt voor de inspiratie die ik uit jullie ervaar. **Arthur, Jessie, Roel, Astrid en Jeroen**. Jullie altijd scherpe analyses en humor hebben gezorgd voor de nodige relativering en steun. Ik hoop dat we als we 80 zijn nog steeds elk jaar in Berlijn Edelweiss zullen zingen. **Btissemme.** Bedankt voor alle etentjes en zinvolle gesprekken over ons werk en leven. **Nienke, Iris, Maayke, Lisa**, er is veel gebeurd ;) sinds wij in (minder) strakke formatie over de Amstel roeiden! Ik ben heel erg blij met onze lange vriendschap. **Ruud, Illy, Sebastiaan, Marjolein, Iris**: een verademing dat het tijdens onze etentjes altijd over politiek gaat en over wat er echt belangrijk is in het leven. Jullie inspireren mij om breder te kijken. Sebastiaan. Bedankt voor je steun in mijn keuze om naar Groningen te gaan. Les Oiseaux Bleus – vrijwilligers, en dan in het bijzonder **Brian, Ans en Hamza**, over inspiratie gesproken. Jullie hebben vele bruggen geslagen en dat is voor mij een prachtig voorbeeld.

Ward, ik ben heel dankbaar dat jij er bent.

Maarten en Sam, ik kan me geen lievere broer en schoonzus bedenken, **Bernard en Jenneke, Selma, Charlotte, Jurriaan, Jonathan, Rogier en Ting:** bedankt voor de onvoorwaardelijke liefde die ik zo vaak uit jullie heb ervaren. **George en Carolien**: Jullie hebben mij voorgeleefd hoe je liefde en dankbaarheid de boventoon laat voeren in het leven. Heel erg bedankt dat jullie mij vrijheid geven, maar er tegelijkertijd altijd zijn als het nodig is.

Hoe, na een geweldig PhD-traject in Groningen en Edinburgh, toepasselijker te eindigen dan door te refereren aan Oma Hanzon: 'Immers…thuisblijvers hebben altijd ongelijk.'

List of publications

Gelauff JM, Rosmalen JGM, Gardien J, Stone J, Tijssen MAJ. Shared demographics and comorbidities in different functional motor disorders. *Parkinsonism Relat Disord*. 2020;70:1–6. doi:10.1016/j.parkreldis.2019.11.018

Gelauff JM, Carson A, Ludwig L, Tijssen MAJ, Stone J. The prognosis of functional limb weakness: a 14-year case-control study. *Brain*. 2019;142(7):2137–2148. doi:10.1093/brain/awz138

Dreissen YEM, Dijk JM, Gelauff JM, et al. Botulinum neurotoxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomised placebo-controlled trial with an open-label extension. *J Neurol Neurosurg Psychiatry*. 2019;90(11):1244–1250. doi:10.1136/jnnp-2018-320071

Zutt R, Elting JW, van Zijl JC, et al. Electrophysiologic testing aids diagnosis and subtyping of myoclonus. *Neurology*. 2018;90(8):e647–e657. doi:10.1212/WNL.0000000000004996

Gelauff JM, Kingma EM, Kalkman JS, et al. Fatigue, not self-rated motor symptom severity, affects quality of life in functional motor disorders. *J Neurol*. 2018;265(8):1803–1809. doi:10.1007/s00415-018-8915-7

Gelauff J*, Zutt R* , Smit M, van Zijl JC, Stone J, Tijssen MAJ. The presence of depression and anxiety do not distinguish between functional jerks and cortical myoclonus, Parkinsonism Relat Disord. 2017 Dec;45:90-93.*shared first

Gelauff J, Stone J. Prognosis of functional neurologic disorders. Handb Clin Neurol. 2017. Gelauff JM and Stone J. Approach to the patient with functional neurological symptoms. Practical Neurology 2017. Fifth edition, edited by José Biller

van Egmond ME, Weijenberg A, van Rijn ME, et al. The efficacy of the modified Atkins diet in North Sea Progressive Myoclonus Epilepsy: an observational prospective open-label study. *Orphanet J Rare Dis*. 2017;12(1):45. Published 2017 Mar 7. doi:10.1186/s13023-017-0595-3

van Gils A, Schoevers RA, Bonvanie IJ, Gelauff JM, Roest AM, Rosmalen JG. Self-Help for Medically Unexplained Symptoms: A Systematic Review and Meta-Analysis. *Psychosom Med*. 2016;78(6):728–739. doi:10.1097/PSY.0000000000000325

Lehn A, Gelauff J, Hoeritzauer I, et al. Functional neurological disorders: mechanisms and treatment. *J Neurol*. 2016;263(3):611–620. doi:10.1007/s00415-015-7893-2

Stone J, Hoeritzauer I, Gelauff J, et al. Functional Disorders in Neurology: Case Studies. *Neurol Clin*. 2016;34(3):667–681. doi:10.1016/j.ncl.2016.04.013

Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. *J Neurol Neurosurg Psychiatry*. 2014;85(2):220–226. doi:10.1136/jnnp-2013-305321

Gelauff JM, Dreissen YE, Tijssen MA, Stone J. Treatment of functional motor disorders. *Curr Treat Options Neurol*. 2014;16(4):286. doi:10.1007/s11940-014-0286-5

Gelauff JM, van Tricht M. Functionele bewegingsstoornissen. Neuropraxis 2014;18(2):67-73.

Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. J Neurol Neurosurg Psychiatry. 2014;85(2):220-6.

Buijink AW, Gelauff JM, van der Salm SM, Tijssen MA, van Rootselaar AF. Jerky periods: myoclonus occurring solely during menses. *Tremor Other Hyperkinet Mov (N Y)*. 2013;3:tre-03-163-3723-1. Published 2013 Apr 26. doi:10.7916/D83X85C9

Stone J, Gelauff J, Carson A. A "twist in the tale": altered perception of ankle position in psychogenic dystonia. Mov Disord. 2012;27(4):585-6.

Curriculum Vitae

Jeannette Gelauff werd geboren op 9-11-1987 en is opgegroeid in Rijswijk. Ze had een leuke en dynamische studententijd aan de Universiteit van Amsterdam, roeide 2 jaar bij Nereus en was actief lid van studentedebatvereniging Bonaparte en studievereniging Mozaïek, onder andere als bestuurslid. Ook is zij sinds haar studietijd vrijwilliger bij stichting Les Oiseaux Bleus, die zich inzet voor gehandicapte kinderen in Tunesië.

Haar interesse voor functionele stoornissen werd gewekt toen zij als onderdeel van het Honours Program meeliep met een patiënte met een functionele bewegingsstoornis, die werd behandeld door dr Gerty Casteelen, psychiater. Deze interesse werd verder aangewakkerd door prof. dr. Rien Vermeulen, neuroloog, die in zijn colleges veel aandacht besteedde aan functionele stoornissen.

Jeannette deed haar wetenschappelijke stage op de afdeling klinische neurofysiologie van het AMC, waar zij samen met Arthur Buijink corticale evoked potentials onderzocht bij patiënten met corticale myoclonus en schrijfkramp. Tijdens deze stage merkte ze dat het vakgebied van bewegingsstoornissen bij uitstek geschikt is voor het bestuderen van het grensvlak tussen neurologie en psychiatrie en leerde ze Marina de Koning-Tijssen kennen. Voor haar coschappen liep ze 3 maanden stage bij dr. Jon Stone en wat later de FRG (Functional Research Group) zou gaan heten, in Edinburgh.

Na haar studie kreeg ze de kans om aan de Rijksuniversiteit Groningen als promovenda haar passie voor functionele stoornissen verder uit te diepen, onder begeleiding van prof. dr. Marina de Koning-Tijssen en prof. dr. Judith Rosmalen in samenwerking met dr. Jon Stone en dr. Alan Carson in Edinburgh. Tijdens het PhD-traject in Groningen en Edinburgh bezocht ze verschillende (inter)nationale congressen waar ze haar onderzoeksresultaten mocht presenteren en organiseerde ze samen met de onderzoeksgroep bewegingsstoornissen verschillende patiëntendagen en cursussen.

Inmiddels is Jeannette met veel plezier begonnen aan de opleiding tot neuroloog in het VUmc. Jeannette hoopt in de toekomst haar klinische werk als neuroloog te blijven combineren met wetenschappelijk onderzoek op het gebied van functionele stoornissen.